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# AMERICAN JOURNAL OF DISEASES OF CHILDREN

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# American Journal of Diseases of Children

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No. 1

## CONGENITAL DEXTROCARDIA WITH PATENT INTER-VENTRICULAR SEPTUM

WITH FLUOROSCOPIC AND ELECTROCARDIOGRAPHIC EXAMINATION \*

RUDOLPH DURYEA MOFFETT M.D., AND SELIAN NEUHOF, M.D.  
NEW YORK

Congenital dextrocardia is an exceedingly rare condition (Foggie, Graanboom and Osler), one of us (Moffett) being able to find only 126 cases reported in a review of the literature from the year 1649. The exact cause for this malposition does not seem to be clear, though numerous investigators (Pegroux, Kussmaul, Winslow and Maschkox, Seres and Sabatier, Selon Dareste, Fol and Waryuski, von Baer, Bischoff and others) have suggested various theories for this abnormality. The most prominent theory (suggested by Fol and Waryuski) is that in the prenatal development of the heart, the right side develops more rapidly than the left and pulls the heart to that side. No theory is sufficiently convincing to explain all cases. Cases of complete transposition of all the organs are numerous, but dextrocardia alone, as in our case, is exceedingly rare. Almost all of the cases of dextrocardia alone that have been reported present symptoms of congenital defects of the heart itself. This has been corroborated by frequent necropsy reports (Ziegler, Fussell, Probyn-Williams, Ewald, Theremin, Keith, Hochsinger and others). It is interesting to note that most of the cases that have been observed are in the male sex—our case was that of a male child. The early cases of pure dextrocardia were merely clinical reports, but about the middle of the nineteenth century the first postmortem records appear. Schroetter<sup>24</sup> reported a case in 1870 and gave a complete review of the subject.

### CASE REPORT

The subject of this paper, D. L., a boy (History No. 3861, 1914, History No. 3009, 1915), came under our observation on Oct. 17, 1914, at the German Hospital Dispensary, New York. The family history is as follows: Number of children living, 7; number of deaths or miscarriages, 3; no history of tuberculosis, rheumatism or syphilis.

\* Submitted for publication April 28, 1915.

The previous history of the patient is the following: He was the ninth child, born on the ninth month, the birth being normal: the birth-weight was not recorded. He had had measles and whooping cough during his second year; his appetite was always good; the bowels were regular; no vomiting occurred. He had been breast-fed until the fourteenth month, and then was put on solid food. The mother said that the child had always been "blue" and "short of breath," but never sufficiently dyspneic to remain in bed. When the child was first seen (Oct. 17, 1914) he was  $3\frac{1}{2}$  years old and had been brought to the dispensary because of a persistent cough which had lasted several months; the cough was worse during the day while the child was up and about. There were no other symptoms that the mother recognized. Physical examination showed a well-nourished child of  $3\frac{1}{2}$  years, with blue lips, active movements of the alae nasi and breathing with its mouth open. The eyes and teeth were normal, but there was blueness and congestion of the blood vessels of the conjunctiva. The hands, feet and lips were distinctly cyanotic; there was distention of the superficial veins of the chest; no thyroid or thymus enlargement; fingers and toes were clubbed (Fig. 1). Weight,  $22\frac{1}{2}$  pounds; length of body, 32 inches; circumference of head,  $18\frac{1}{2}$  inches; of chest,  $19\frac{1}{2}$  inches; of abdomen 20 inches.

Lungs: Over the entire anterior and posterior surface of the chest there were many loud, moist râles; there was no dulness or increase in the breath or voice sound.

Heart: On inspection there was a vigorous heaving systolic impulse in the right axillary line and in the epigastrium. On palpation, there was a strong, marked, systolic thrill felt over the entire precordium, but most marked and roughest at the lower end of the sternum and in the epigastrium. The apex beat was felt most prominently 6.5 cm. to the right of the midsternal line; on percussion, the left border was at the left sternal margin.

The right border in the sixth space was 9 cm., in the fifth space 8 cm., in the fourth space 7 cm., in the third space 5 cm., and in the second space 3 cm. to the right of the midsternal line. The nipple was 6 cm. to the right of the same line.

Corresponding to the area of palpable thrill there was a loud, rough systolic murmur. This murmur, less loud and less distinct, could be heard over the entire chest, anteriorly and posteriorly. It could also be heard in the great vessels of the neck. There was no Gerhardt's area of dulness in the second and third right interspaces. The pulse was 108 per minute; respiration, 28; abdomen, distended; liver and spleen in normal position, but somewhat enlarged, the liver being 7 cm. below the costal margin. Roentgenographic examination of patient Jan. 6, 1915, revealed the following findings:<sup>1</sup>

"The bony structures were first examined and it was found that except for some anomalous changes in the metacarpals, the osseous structure seemed normal. The left metacarpals (Fig. 2) when compared with the right were found to be short, thickened and club shaped, although the natural bone structure seemed to be normal.

"Taking up the thorax next, we found that we were dealing with a case of pure dextrocardia (Fig. 3). What under normal conditions would be considered the left heart was markedly enlarged and occupied at least two-thirds of the right chest cavity.

"Further investigation particularly to ascertain the position of the gastrointestinal tract, revealed the stomach in its normal position (Fig. 4) under the left diaphragm with the liver under the right. The injection of a bismuth solution into the colon per rectum gave us normal observation as to the location and size of the large intestine. The marked contraction seen in the middle third of the stomach we believe to be due to spasm.

1. Since the preparation of this report the patient died, but no postmortem examination was obtainable.



Fig. 1.—Patient's hands. Note clubbing of fingers.



Fig. 2.—Changes in bones of hand are clearly shown.

"Conclusions: The case is then one of pure dextrocardia in a child with a tendency toward anomalous development, which is shown by malformation of the metacarpals."

In addition to the physical signs already described, diagnostic data were also furnished by careful fluoroscopic study of the heart and an orthodiascopic tracing of its outline. By fluoroscopy, a distinctly

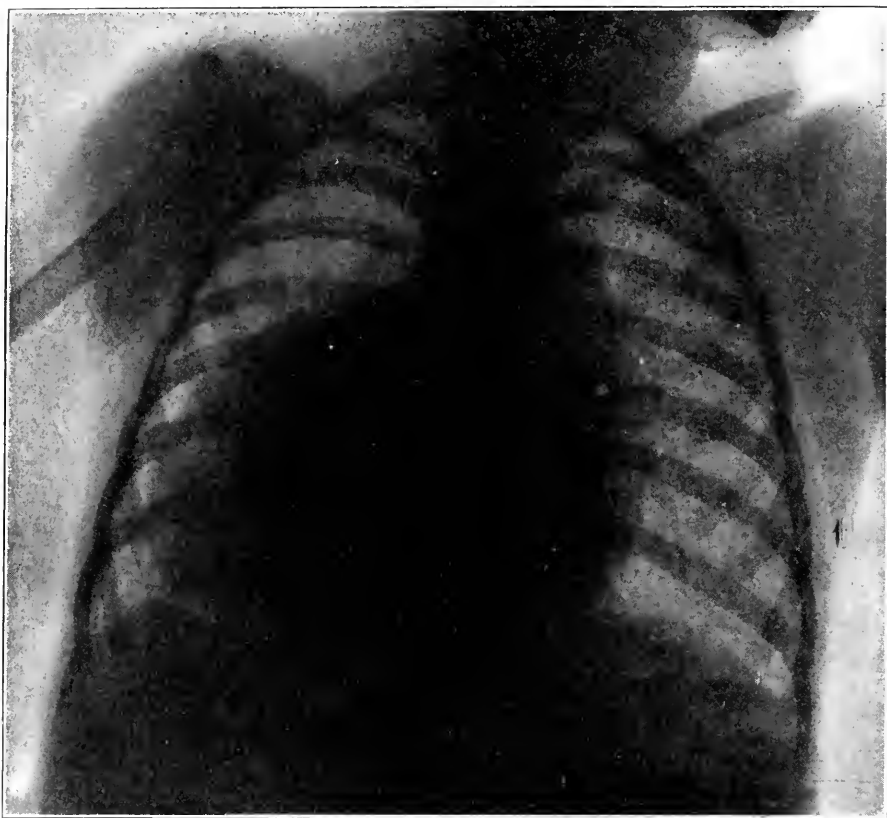


Fig. 3.—Roentgenogram showing dextrocardia.

enlarged and vigorous pulsating aorta was visible (Fig. 5). Beneath it, the pulsating area usually occupied by the pulmonary artery was not visible. In its stead, there was found a hugely dilated, prominent and "knob-like" left<sup>2</sup> auricle. The "left" ventricular shadow was also very much enlarged; its area could not be definitely distinguished from the "left" auricle, though their non-synchronous pulsations could

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2. In this description in order to avoid confusion "left" and "right" are used in the sense as usually applied to the normal heart in its normal position, that is, "left" will refer to the larger and "right" to the smaller cavities of the heart.



be readily determined. The "right" auricle was enlarged. Beneath it, the beginning of the "right" ventricular shadow was seen deeply depressing the diaphragm during inspiration; from this it seemed probable that the entire "right" ventricle was enlarged. A comparison with the orthodiascopic tracing of a case of dextrocardia with no congenital defects (Fig. 6) and with normal cardiac outlines will serve to bring



Figure 4.—Roentgenogram showing stomach in normal position.

into sharper contrast the abnormalities described. The deviations in the first lead (the symmetrical lead) of the electrocardiogram (Fig. 7*b*) were all downward, an infallible electrocardiographic evidence of congenital dextrocardia (Neuhof<sup>148</sup>). Unfortunately, the second and third leads, though taken and studied, were subsequently lost. They showed runs of paroxysmal auricular tachycardia lasting several or many beats, with very much shortened auriculoventricular conduction time; the usual "onset" of paroxysmal tachycardia—an initial beat appearing after a compensatory pause (Lewis) was absent; in a

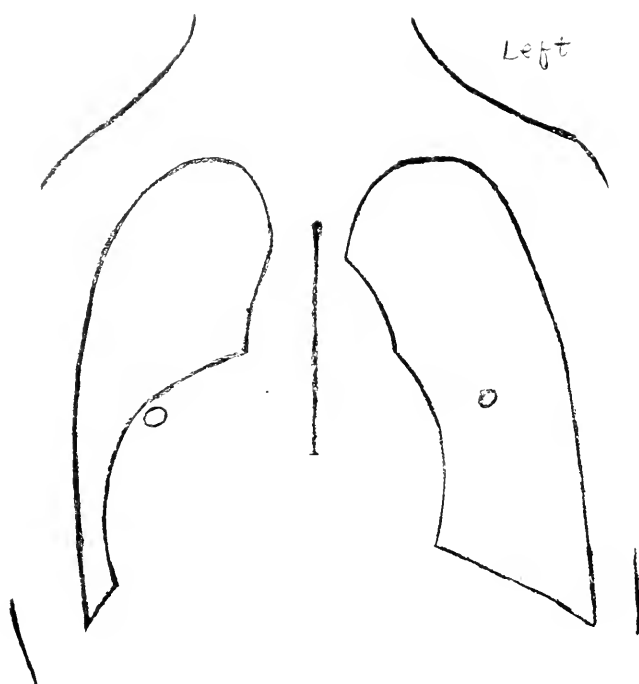


Fig. 5.—Orthodiascopic tracing of the patient with dextrocardia.

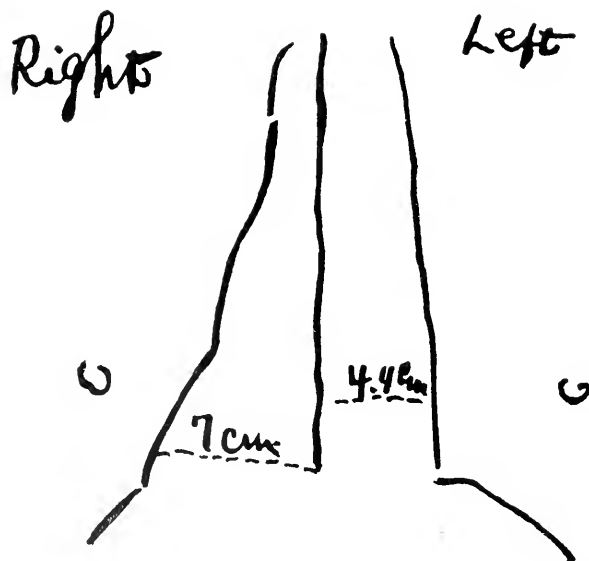


Fig. 6.—Orthodiascopic tracing of a case of dextrocardia with a normal heart for comparison with Fig. 5.

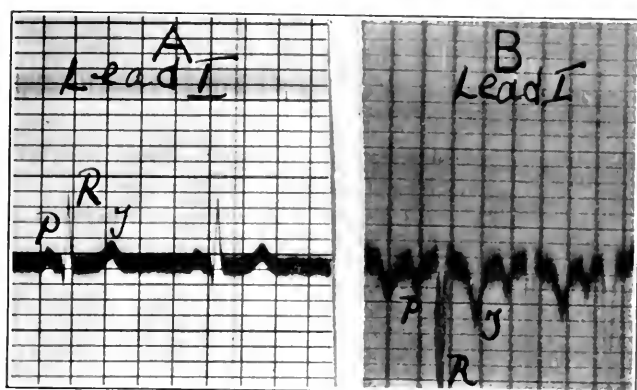


Fig. 7.—*A*, electrocardiogram (Lead I) of patient with heart in normal position. The deviations P, R and T are positive. *B*, electrocardiogram (Lead I) of the patient, D. L. The deviations P, R and T are negative. P is the auricular, R and T the ventricular complex.

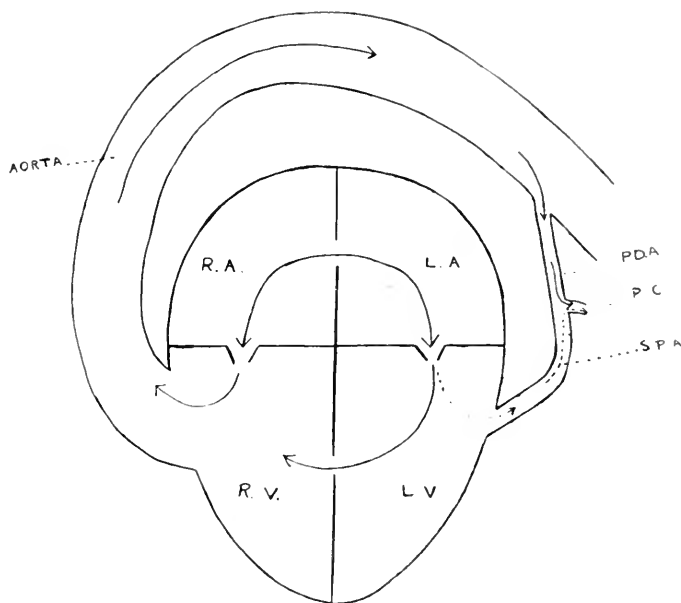


Fig. 8.—Diagram of probable cardiac circulation in the patient D. L. Solid arrows, main circulation; dotted arrows, minor circulation; R.A., right auricle; RV, right ventricle; L.A., left auricle; LV, left ventricle; PDA, patent ductus arteriosus; PC, pulmonary circulation; SPA, stenosed pulmonary artery.

section of the tracing, the normal rhythm was preceded by a compensatory pause (offset). A large deviation (the representative of an auricular beat) was present in Lead 2; this is usually regarded as evidence of "left" auricular hypertrophy.

A correlation of the physical and fluoroscopic signs—thrill and murmur over the entire precordium but most prominent at the xiphoid; apparent absence of the radiographic shadow of the pulmonary artery; an enlarged "left" auricle; an enlarged "right" auricle, "left" and probably also "right" ventricle point toward patent foramen ovale and interventricular septum as the probable congenital lesions. Orthodiagnostic evidence of a patent ductus arteriosus was not found, but if the diagnosis of septal defects and pulmonary stenosis be correct, it is safe to assume that a patent duct was present; otherwise there would be no outlet for the blood necessary for pulmonary circulation, as evidenced by the diagram (Fig. 8) representing the probable directions of the blood current. These anomalies—pulmonary stenosis and patent ductus arteriosus—are not infrequently associated with septal defects (Carpenter,<sup>150</sup> von Rokitsansky<sup>151</sup>). In a postmortem specimen of a heart normally placed in the chest (examined through the courtesy of Dr. B. S. Oppenheimer) septal defects and anomalies like those described were present; the ductus arteriosus was short, not dilated, and was surrounded by adhesions. If similarly distorted in our case, it would sufficiently account for the fact that it was not discovered during fluoroscopy.<sup>3</sup>

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#### BIBLIOGRAPHY

The following is a collection of cases cited from the literature, complete so far as possible from the year 1649. The cases given are of pure dextrocardia. Cases in which the liver and spleen were in abnormal position are not reported.

Lit. No.	Case No.	Year	Reference
1	1	1649	Riolani: <i>Anthropographia</i> , cited by Otto as pure dextrocardia; not cited by other authors.
2	2	1671	Moellenbrock: <i>Miscellanea Curiosa</i> , necropsy report; cited by a number of authors as true dextrocardia; Foggie says that the stomach also lay a little to the right.
3	..	1671	Hoffman: <i>Cardianstrophe admiranda seu cordis inversio</i> . Cited by Otto as true dextrocardia; Krieger states that this is the same case as Moellenbrock's.
4	3	1769	Eschenbach: <i>Observata anatom. chir. med. rariora</i> . One case found at necropsy; also cited by Krieger and Vehsemeyer.

3. Roentgenographic examination by Dr. William H. Stewart of the German Hospital and Dispensary, whom we desire to thank for his examination.

Lit. No.	Case No.	Year	References
5	4	1793	Abernethy: Tr. Philosoph. Soc., London, p. 59. One case cited by a number of authors as true dextrocardia; Foggie states that the liver lay in the middle line.
6	5	1816	Otto: Seltene Beob. z. Anat., Physiol. u. Path. Two cases, one found during life and confirmed at necropsy; one necropsy of a child. See also 1829, Otto.
7	6	1824	Würsburger Pathologisches Institut, necropsy, also cited by Mosler, 1866, and a number of other authors.
8	7	1826	Meckel: Archiv. f. path. Anat. u. Physiol., p. 41. One case in a premature child with complete absence of the right lung. Cited by a number of authors.
9	8	1826	Breschet: Repert. gen. d'Anat., 2:1. Gives four cases, only two of which are accepted by Schroetter, 1887, and three by Krieger.
10	9	1829	Otto: Neue seltene Beobacht. z. Anat., Physiol. u. Path. A third case. See Otto, 1816.
11	10	1832	Geoffroy-St-Hilaire: Histoire gén. et partic. d. Anom. d. l'Organisation. Cites no new case; reviews those of other authors cited above.
12	11	1834	Lepington: London Med. Gaz., xv, 228. Heart on right side, serous effusion in lungs; gall-bladder absent. Dextrocardia possibly congenital, author does not state.
13	12	1836	Cooper: London Med. Gaz., xviii, 600. Dextrocardia with malformations of the thoracic viscera, cited by several authors as congenital, although Foggie states that it was a sequel to a right-side pleurisy of fetal origin.
14	13	1849	Cruveilhier, J.: Traité d'Anat. path. gen. One case of heart displaced to right by a diaphragmatic hernia.
15	14	1854	Stokes: Diseases of the Heart and Aorta. One case of heart displaced to right by a diaphragmatic hernia.
16	15	1857	Aertz: Bericht d. allg. Krankenhaus z. Wien. One case, cited by Velssemeyer and Becker.
17	16	1858	Peacock: On Malformations of the Human Heart. Cited two cases, clinical diagnosis only, in which liver lay on left side; position of other organs not stated. Not cited by other authors.
18	17	1862	Maschka: Allg. Wien. med. Ztg., vii, 78. One case with patient's right lung absent; necropsy on newborn child; also cited by Foggie.
19	18	1863	MacLean: Lancet, London, 1863, ii, 159. Liver also transposed; position of other organs not stated.
20	19	1861	Jasinski: Wien. Med.-Haller, ii, 323. One case.
21	20	1866	Mosler: Berl. klin. Wehnschr., No. 21. Cites the Würzburger (1824) case; also one case of his own clinical diagnosis only; both cases accepted by Velssemeyer and Becker, only the first by Lochte.
22	21	1869	Alvarenza: Jour. d. méd., de chir. et de pharmacol., Nos. 47 and 48. Not obtainable; according to title a case of "trochocardia."
23	22	1869	Bailey: Tr. Obst. Soc., x. Case with diaphragmatic hernia; also cited by Foggie.
24	23	1870	Schroetter: Jahrb. d. klin. Gesellsch. d. Aerzte, Parts 5 and 6; also in Med. Jahrb., xx, 189. One case which the author considers congenital with added traction from a diseased right lung. Also cited by other authors.
25	24	1871	Rodriguez: Gac. Med. d. Mex. Title reads "Transposition of Viscera," but the United States Surgeon-General's catalogue classifies it under displacements of the heart, and not under viscera; original not obtainable.
26	25	1873	Bienfait: Bull. Soc. Méd. d. Reims, p. 76. Title, "Dextrocardia," does not indicate whether congenital or not. Not obtainable.

Lit. No.	Case No.	Year	References
27	..	1875	Accolas: Jour. d. méd. et de chir. prat., xvi, 258. Title, "Transposition of the Heart to the Right," does not indicate whether congenital or not. Article not obtainable.
28	22	1877	Falck: Greifswald University Thesis. Title: Ein Fall von congenitaler Dextrocardia.
29	23	1877	Paganuzzi: Gior. veneto di Sc. med., Series 3, xxvii, 31. According to title, true dextrocardia.
30	24	1877	Mosler: Deutsch. med. Wehnschr., iii, 301. Mosler's second case; see 1866. Cited by a number of other authors.
31	25 26	1880	Krieger: Berlin University Thesis. Title: Zur Geschichte der congenitalen Dextrocardia. Cites one case from Leichenstern, not published elsewhere; also a case of his own, both congenital; cited by Foggie.
32	27	1881	Bramwell: Edinburgh Med. Jour., xxvii, 743. One case; also cited by Foggie.
33	..	1881	Robinson: Bull. New York Path. Soc., Series 2, i, 48. One case with cor biloculare and liver on left side; other organs normal; necropsy; also cited by Foggie.
34	28	1881	Ziemssen: Ann. d. stadt. allg. Krankenh. München. One case; also cited by Vehsemeyer and Becker.
35	29	1882	Pope: Lancet, London, 1882, ii, 9. One case, clinical diagnosis and necropsy; cited by a number of other authors.
36	30 31	1882	Wehn: Würzburg University Thesis. Title: Beiträge Zur Heterotaxie de Eingeweide. Includes two cases of true congenital dextrocardia, cited by a number of other authors.
37	..	1883	Küchenmeister: Die angeborene, vollständige seitliche Verlagerung der Eingeweide. Cites no new cases; discusses the subject.
38	32	1887	Schroetter: Berl. klin. Wehnschr., xxiv, 448. One case of his own; also the one later described by Kundrat, 1888. Both cited by a number of other authors.
39	33	1887	Süssman: München. med. Wehnschr., xxxiv, 991; 1014. One case; cited by a number of other authors.
40	34	1888	Kundrat: Verhndl. d. Gesellsch. d. Aerzte in Wien. One case; also described by Schroetter, and cited by a number of other authors.
41	35	1888	Gruss: Wien. med. Blätt., p. 202; also Berl. klin. Wehnschr., No. 8. One case, considered congenital by author; see also Pal, 1907, cited by a number of other authors.
42	36	1888	Bamberger: Wien. med. Blätt., p. 205. One case, considered congenital by author; later described by Pascheles, 1897, and Paltauf, 1901.
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44	38	1888	Chabrely: Jour. d. méd. d. Bordeaux, xviii, 16. One case with both lungs diseased, no attack of pleurisy; lung disease possible cause of dextrocardia, but author considers it probably congenital.
45	39	1888	Michel: Med. Rec., xxxiv, 479. One case.
46	40	1889	Grünfeld: Prag. med. Wehnschr., xiv, 2. One case; also cited by other authors.
47	41	1889	Reddingius: Nederlandsch Tijdschr. v. Geneesk., No. 15. One case, necropsy; also cited by Vehsemeyer and Becker.
48	..	1890	Holt: Arch. Pediat., vii, 81. One case with enlarged right ventricle believed by author to be the cause of the displacement.

Lit. No.	Case No.	Year	References
49	42	1890	Grunmach: Berl. klin. Wehnschr., xxvii, 22. One case; pulmonary stenosis. Cited by a number of other authors as true dextrocardia.
50	..	1890	Niesel: Deutsch. med. Wehnschr., xvi, 499. One case with a right-side pleurisy, not certainly congenital, but probably so; regarded by Vehsemeyer as congenital.
51	43	1890	Adie: Indian Med. Gaz., xxv, 117. One case, clinical diagnosis, persistent cough, but no symptoms of lung disease severe enough to cause the dextrocardia; probably congenital.
52	44	1890	Graanboom: Ztschr. f. klin. Med., xviii, 185. One case; also cited by a number of other authors.
53	45	1890	Cipriani: Lo Sperimentale, lxvii, 127. One case, clinical diagnosis and necropsy; also cited by Foggie.
54	46	1890	Sandhop: Greifswald University Thesis. Title: Ein Fall von kongenitaler Dextrokardie. One case; also cited by Nagel.
55	47	1891	Arnaud: Compt. rend. Soc. de biol., Series 9, iii, 4. One case.
56	..	1891	Inches: Maritime Med. News, iii, 63. One case; author doubtful whether congenital or caused by lung disease.
57	48	1891	Schott: Therap. Monatsh., v, 270. One case; also cited by a number of others; clinical diagnosis only.
58	..	1891	Varsi: An. Asist. púb., Buenos Aires, ii, 46. Not obtainable. Title: "A Case of Dextrocardia." Does not indicate whether congenital or not.
59	49	1891	Becker: Jena University Thesis. Title: Ueber Dextrocardia. One case; also cited by Nagel and Foggie as true dextrocardia.
60	50	1891	Hawkins: Tr. Clin. Soc., London, xxiv, 250. One case with pulmonary stenosis, but considered congenital by author; also by Foggie.
61	..	1891	Ewart and Bennett: Tr. Med. Soc., London, xiv, 438. One case, doubtful whether congenital or due to contraction of right lung.
62	51	1892	Heimann: Berl. klin. Wehnschr., xxix, 188. One case showing misshapen chest and other congenital faults; also cited by Foggie.
63	52	1892	Berwald: Berl. klin. Wehnschr., xxix, 1022. One case, clinical diagnosis and necropsy; also cited by Foggie.
64	53	1892-93	Bard: Lyon méd., lxxi, 583; lxxii, 15. One case with mitral stenosis; clinical diagnosis; also cited by Foggie and Loewenthal.
65	54	1894	Lochte: Beitr. z. path. Anat. u. z. allg. Path., xvi, 189. One case found at necropsy; also cited by Foggie.
66	55	1894	Stren: Norsk Mag. f. Laegevidensk., 4 R., ix, 93. One case; cited also by Vehsemeyer.
67	56	1894	Perregaux and Morestin: Bull. Soc. anat. d. Paris, lxiv, 968; 983. One case, clinical diagnosis and necropsy; right lung flattened and misplaced; also cited by Foggie.
68	57	1894	Droog: Nederl. Tijdschr. v. Geneesk., 2 R., xxx, Part 1, 872. One case; also cited by Loewenthal.
69	..	1894	Kreisch: Bonn University Thesis. Title: Ein Fall von hoch gradiger Verlagerung des Herzens in die rechte Seite. One case with enlargement of the left lung which may have caused the dextrocardia.
70	58	1894	Schroetter: Wien. med. Presse, Nos. 1 and 2. One case also cited by Loewenthal.
71	59	1894	Schmidt-Monnard: München. med. Wehnschr., xli, 584. One case; also cited by Loewenthal.
72	60	1895	Campbell: Montreal Med. Jour., xxiv, 515. One case, probably congenital; deformity of right chest caused by accident in childhood.

Lit. No.	Case No.	Year	References
73	61	1895	Goryanski: <i>Boln. Gaz. Botkina</i> , iii, 369. One case, probably congenital.
74	62	1896	Gerard: <i>Lancet</i> , London, Vol. 1 for 1896. One case; also cited by Loewenthal and Foggie.
75	63	1896	MacLennan: <i>Brit. Med. Jour.</i> , Vol. 2 for 1896, p. 1314. One case; also cited by Loewenthal and Foggie.
76	..	1896	Fernet: <i>Bull. et mém. Soc. méd. d. hôp. d. Paris</i> , Series 3, xiii, 873. One case probably due to autenatal pleural disease, or disease in early infancy.
77	64	1896	Berks: <i>Wien. klin. Rundschau</i> , x, 497. One case; also cited by Foggie.
78	65	1896	Bramwell: <i>Atlas of Clinical Medicine</i> , iii, 116. One case with pulmonary stenosis, probably congenital; also cited by Foggie.
79	..	1896	Sobierajczyk: <i>Berlin University Thesis</i> . Title: <i>Zur Casuistik der Dextrocardie</i> . Same case as described by Velsmeyer, 1897.
80	66	1897	Vehsemeyer: <i>Deutsch. med. Wechschr.</i> , xxiii, 180. Case diagnosed by Roentgen ray; also cited by others.
81	67	1897	Wardrop-Griffith: <i>Brit. Med. Jour.</i> , Vol. 1 for 1897, p. 1287. One case considered congenital, with pulmonary stenosis.
82	..	1897	Pascheles and Paltauf: <i>Wien. klin. Rundschau</i> , xi, 473. Later report on Bamberger's (1888) case. See also Paltauf 1901.
83	68	1897	Auché and Bouyer: <i>Jour. d. méd. d. Bordeaux</i> , xxvii, 413. One case.
84	69	1898	Petit and Ravaut: <i>Bull. et mém. Soc. méd. d. hôp. de Paris</i> , Series 3, xv, 195; also in <i>Gaz. d. Hôp.</i> , lxxi, 293. One case; also cited by Foggie.
85	70	1898	Berend: <i>Gyermekgyogyaszat</i> , p. 16. One case.
86	71	1898	Kroenig: <i>Berl. klin. Wechschr.</i> , pp. 230, 466. One case, clinical report and necropsy, with abnormal breadth of left lung; regarded by author as congenital; also cited by Schwalbe and Loewenthal; questioned by Foggie.
87	72	1898	Middleton: <i>Glasgow Med. Jour.</i> , i, 244. One case with other congenital deformities, but no other viscera transposed; also cited by Foggie.
88	73	1899	Geipel: <i>Festschr. z. Feier d. 50 jähr. Bestehens d. Stadtkrankenhauses z. Dresden-Friedrichstadt</i> , p. 373. One case, clinical diagnosis and necropsy; also cited by Nagel.
89	74	1899	Leo: <i>Jahrb. f. Kinderh.</i> , new series, 1, 427. One case; also cited by Foggie.
90	75	1900	Bonheim: <i>Kiel University Thesis</i> . Title: <i>Ueber Dextrocardia</i> . One case, with other congenital defects; also cited by Foggie and Schwalbe.
91	76	1900	Crispino: <i>Riforma med.</i> , xvi, Part 3, 436, 447, 459. One case, clinical diagnosis; also cited by Foggie.
92	77	1900	Schmilinsky: <i>Deutsch. med. Wechschr.</i> , xxvi Ver. Beil., 194. One case, clinical diagnosis; also cited by Foggie and Nagel.
93	78	1900	Chapman: <i>Intercolonial Med. Jour.</i> , v, 309. One case; also cited by Foggie.
94	79	1900	Loewenthal: <i>Ztschr. f. klin. Med.</i> , xli, 170. One case, clinical diagnosis and necropsy; also cited one case reported by Senator in 1899 (reference not given), clinical diagnosis by Roentgen ray.
95	80	1901	Monks: <i>Brit. Med. Jour.</i> , Vol. 1 for 1901, p. 514. One case; also cited by Foggie.
96	81	1901	Baudouin: <i>Gaz. méd. d. Paris</i> , Series 12, i, 33. Cites no new case; discusses theory.



Lit. No.	Case No.	Year	References
97	82	1901	Chapot-Prevost: <i>Compt. rend. Acad. d. sc.</i> , cxxxii, 223. Congenital dextrocardia in one member of a twin monster who lived after operation for separation.
98	83	1901	Paltauf: <i>Wien. klin. Wchnschr.</i> , xiv, 1032. Postmortem of case reported by Bamberger in 1888 and Pascheles, 1897. Shows pericarditis which Paltanf considers the cause of the dextrocardia.
99	84	1901	Weinberger: <i>Wien. klin. Wchnschr.</i> , xiv, 129. One case regarded by author as probably congenital, with symptoms of lung disease, also possibly congenital; cited by Foggie as truly congenital.
100	85	1901	Gossage: <i>Tr. Clin. Soc. London</i> , xxxiv, 220. One case reported by authors as congenital.
101	86	1902	Darnall: <i>Med. News</i> , lxxx, 446. One case.
102	...	1902	Alaux: <i>Lyon University Thesis</i> . Not obtainable; case not described elsewhere.
103	87	1902	Brudziński: <i>Gaz. lek.</i> (Warsaw). One case.
104	88	1902	Baumgarth: <i>Halle University Thesis</i> . Title: <i>Cor biloculare mit Dextrokardie</i> . One case; also cited by Foggie and Nagel. Clinical report and necropsy.
105	89	1902	Wagner: <i>Rostock University Thesis</i> . Title: <i>Zur Kenntnis der erworbenen und angeborenen Rechtslage des Herzen</i> . One case, with facial defect also. Cited by Foggie.
106	..	1903	Beclère: <i>Bull. et mém. Soc. méd. d. hôp. de Paris</i> , Series 3, xx, 559. No case report, discusses diagnosis, chiefly of acquired dextrocardia.
107	90	1903	Wendling: <i>Med. Blätt.</i> , xxvi, 563. One case, clinical diagnosis and necropsy; also cited by Foggie.
108	91	1903	Parkinson: <i>Rep. Soc. Study Dis. Child.</i> , iii, 213. One case.
109	92	1903	Benfey: <i>Berlin University Thesis</i> . Title: <i>Beiträge zur Lehre des Situs Transversus Partialis</i> . One case with pulmonary stenosis, also congenital.
110	93	1903	Flatau: <i>Neurol. Centralbl.</i> , xxii, 643. One case; also cited by Foggie.
111	94	1903	Wright and Drake: <i>Tr. Assn. Am. Phys.</i> , xviii, 272. One case with heart malformation, necropsy; also cited by Schwalbe.
112	95	1904	Carpenter: <i>Brit. Jour. Child Dis.</i> , i, 160. One case, possibly congenital, possibly caused by large cystic left lung; also cited by Foggie.
113	96	1904	Stone: <i>Boston Med. and Surg. Jour.</i> , cl, 29. One case, probably congenital.
114	97	1905	Hoffman: <i>Cor.-Bl. f. schweiz. Aerzte</i> , xxxv, 111. One case, Roentgen-ray diagnosis.
115	98	1905	Mclver: <i>Charlotte (N. C.) Med. Jour.</i> , xxvii, 42. One case.
116	99	1906	Graham: <i>Royal Army Med. Corps Jour.</i> , vii, 498. One case, possibly caused by pulmonary disease.
117	100	1906	Hochsinger: <i>Deutsch. med. Wchnschr.</i> , xxxii, 1607. One case with heart defects, Roentgen-ray diagnosis.
118	101	1906	Neumann: <i>Marburg University Thesis</i> . Title: <i>Ueber ein Fall von Dextrokardie</i> . One case, clinical diagnosis; also cited by Nagel and Foggie.
119	102	1906	Potter, G. W.: <i>Congenital Malformation of Heart, with Malposition of Certain Viscera and Absence of Spleen</i> . <i>Jour. Am. Med. Assn.</i> , Aug. 4, 1906, p. 363. One case, with stomach and intestines in the thorax; spleen absent. Congenital.
120	...	1907	Pal: <i>Wien. med. Presse</i> , xlviii, 809. Necropsy confirming diagnosis of case reported by Gruss in 1888.

Lit. No.	Case No.	Year	References
121	103 104 105 106	1907	Aufdermauer: Zurich University Thesis. Title: Ueber Dextrocardia congenita et acquisita. Reports five cases of congenital dextrocardia, one with right hydrothorax, clinical diagnosis; also cites one necropsy report by Lucchi.
122	107	1907	Tate: Jour. Royal Army Med. Corps, viii, 434. One case Roentgen-ray diagnosis; also cited by Foggie.
123	108	1907	Doolittle: Boston Med. and Surg. Jour., clvii, 662. One case.
124	109	1907	Hawthorn: Brit. Med. Jour., Vol. 1 for 1907, p. 1186. One case with valvular disease, clinical report.
125	110	1909	Schelenz: Berl. klin. Wehnschr., xlv, 788; 840. One case, liver also transposed, other viscera normal.
126	111	1909	Carpenter: Rep. Soc. Study Dis. Child., p. 163; also in Brit. Jour. Child. Dis., vi, 444. Reports briefly one new case and refers to his 1904 case.
127	112	1909	Scandola: Gaz. d. osp. Milan, xxx, 1065. One case.
128	113	1909	Nagel: Deutsch. Arch. f. klin. Med., xcvi, 552. One case, clinical diagnosis and necropsy; tabulates other cases.
129	114	1910	Fossier: New Orleans Med. Jour., lxiii, 542. One case in which the heart was displaced to right when patient was lying on right side (about 6 cm.), apparently congenital.
130	115	1910	Whyte: Brit. Med. Jour., Vol. 2 for 1910, p. 198. One case.
131	116	1910	Foggie: Edinburgh Med. Jour., v, 428. One case with cor biloculare, clinical diagnosis and necropsy; tabulates other cases.
132	...	1910	Schwalbe: Morphologie der Missbildungen des Menschen und der Tiere, Part 3, Section 2, p. 370. Cites no new cases; reviews others.
133	117	1911	Stoerk: Mitt. d. Gesellsch. f. inn. Med. u. Kinderh. One case.
134	...	1911	Host: Norsk Mag. f. Laegevidensk, 5 R., ix, 435. Not obtainable; title does not indicate whether congenital or not.
135	118	1911	Brooks: Med. Rec., lxxix, 962. One case.
136	119	1911	Geissler: Wien. klin. Rundschau, xxv, 565. One case.
137	120	1911	Vandervelde and Catineau: Jour. méd. d. Bordeaux. One case. See also Vandeput, 1912.
138	121	1912	Mohr: Berl. klin. Wehnschr.; also in Münch. med. Wehnschr., No. 7, 387. One case.
139	122	1912	Benjamin: Verhandl. d. München. Gesellsch. f. Kinderheilk.; also in Jahrb. f. Kinderh., lxxv, 367. One case.
140	123	1912	Culcer-Petresco: Paris Thesis. Title: Quelques considérations à propos d'un cas nouveau de dextrocardie congénitale. One case with cardiac malformations, clinical diagnosis, Roentgen-ray. Reviews other cases.
141	...	1912	Bello Moraes: Med. Contemp. (Lisbon), xxx, 190. Not obtainable; title does not indicate whether congenital or not.
142	...	1912	Vandeput: Jour de méd. d. Bordeaux, xvii, 37. Roentgen-ray report of case of Vandervelde and Catineau, 1911.
143	124	1912	Berenguer: Semaine méd. (Buenos Aires), xix, Part 2, p. 549. One case with diaphragmatic hernia.
144	125	1913	Cade, Rebattu and Gras: Province Méd., xxiv, 206. One case, dextrocardia acquired in prenatal life.
145	...	1913	Curti: Gazz. internat. d. med., xvi, 947. Not obtainable. Title does not indicate whether congenital or not.
146	126	1913	Giovannini: Policlin. 20: sez. Prat. 1479. One case.

Lit. No.	Case No.	Year	References
147	...	1913	Hermanides: <i>Nederlandsch. Tijdschr. v. Geneesk.</i> , i, 1471. Not obtainable. Title does not indicate whether congenital or not.
148	...	1913	Neuhof: <i>Post-Grad.</i> , xxviii, 262; A Case of Congenital Familial Dextrocardia, <i>Jour. Am. Med. Assn.</i> , April 5, 1913, p. 1064. Case with patient's liver and spleen also transposed. (Roentgen-ray and electrocardiographic diagnosis.)
149	...	1915	Abbott: <i>Osler's Modern Medicine</i> , ed. 2, iv, 323. Cites no new cases, reviews others.
150	...	1894	Carpenter: <i>Congenital Affections of the Heart</i> , London, p. 16.
151	...	1875	Von Rokitansky: <i>Die defecte der Scheidewande des herzen</i> . Wien, vi, p. 8.

## PATHOLOGY OF MYATONIA CONGENITA (OPPLNHEIM)

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Complete postmortems in cases of this condition have been reported by Spiller, Baudouin, Lereboullet-Baudouin, Collier-Holmes, Rothmann, Beevor and Kaumheimer; Reyher-Helmholz in one necropsy examined only the musculature, and Bing, Collier-Holmes and Skoog respectively, examined a small piece of muscle excised from the patient during life.

The scarcity of the anatomic examinations recorded, especially in the American literature, the only reports given being those by Spiller-Smith and Skoog, justifies the publication here of the results of the examination of pieces of muscle and nerve in the case of myatonia congenita, which I reported in the *AMERICAN JOURNAL OF DISEASES OF CHILDREN*, October, 1914.

Sept. 8, 1914, the baby spoken of in that report became cyanotic while nursing and died suddenly, about one week after my last visit. A necropsy to examine the entire nervous system and the organs of inner secretion and to establish the cause of the sudden death (thymus, bronchitis?), was refused and I had to content myself with the excision of a large piece of the calf musculature throughout its depth, and of the peroneal and popliteal (tibial) nerves of the right leg, two hours after death.

The subcutaneous fat-tissue over the gastrocnemius muscle was about 8 mm. thick. The musculature was markedly pale pink, but apparently of undiminished volume. The specimens were preserved in a 10 per cent. formaldehyd solution and later were examined by Dr. Maximilian Herzog, pathologist of the Cook County Hospital, to whom I am indebted for the following report:

From the muscle removed pieces were embedded in paraffin, sectioned and stained with hematoxylin-eosin. The sections reveal a very advanced and marked condition of atrophy of muscular tissue (Fig. 1). The individual bundles of muscle fibers are small and separated from each other by a large amount of areolar fatty tissue. The latter presents the usual appearance of fat cells. It appears that from one-third to one-half of the entire original muscle tissue is now composed of areolar tissue. The latter appears to be quite vascular. Examination even under low power already shows enormous increase of sarcolemma-nuclei.

Under oil-immersion magnification it is seen that the muscle fibers left do not show well the normal striation; it is particularly the longitudinal striation

which is indistinct. On the other hand, the transverse striation in some places at least, is unusually distinct and it appears that the dark lines between the disks are widened (Fig. 2).

The muscle fibers are in cross-sections narrow, round or oval and vary in size (Fig. 3). No hypertrophic fibers are present. The vessels in the interstitial and areolar connective tissue appear to be numerically increased and perhaps enlarged in size, but there is no marked thickening of their walls. The sarcolemma-nuclei under the high power show oval or round with a considerable amount of chromatic substance. In some places indications of karyokinetic figures can be seen. It is very evident that the great numbers of sarcolemma-nuclei and the karyokinetic figures indicate an attempt at regeneration or new formation. Of the sarcolemma-nuclei which are so numerous found in the



Fig. 1.—Muscle bundles small, separated by proliferated connective and by areolar fatty tissue; enormous increase of the number of sarcolemma-nuclei. From microphotograph,  $\times 60$ .

sections, the majority have retained their normal relation directly under the sarcolemma itself, but here and there one sees places in the sections where the nuclei are found in the sarcoplasm itself, even in its very center. This of course is the condition which we generally see in regenerating voluntary muscle fibers. The development of the muscle appears to be retarded, presenting a prenatal stage, the not developed fibers being replaced by areolar tissue.

Peripheral nerves stained by Weigert's method, show marked, but not very profound degenerative changes. On the whole the myelin sheath is well preserved, but here and there it is thinned out and reduced to a very thin mantle of the axis-cylinder. One also occasionally sees breaks in the myelin sheath and the interspaces at the nodes of Ranvier are increased in size. There has

not been much proliferation of neurilemma nuclei, but the ordinary connective tissue between the individual bundles of nerve fibers is very much increased, so that the peroneal nerve contains more fibrous connective tissue than nerve tissue proper (Fig. 4).

Correlating the clinical findings with the pathologic findings described above, the profound atrophy and the decreased number of the muscle fibers explain the paralysis; the intense proliferation of the connective and fatty tissue, infiltrating and replacing the muscle substance, made the muscle appear of normal volume and concealed the



Fig. 2.—Transverse striation unusually distinct; atrophic fibers; no hypertrophic fibers. From microphotograph,  $\times 1,000$ .

actual atrophy; the flabbiness of the musculature and the striking impossibility of distinguishing the muscle from the panniculus adiposus by palpation, as reported in the clinical history of the case, are the result of the same pathologic condition.

#### MUSCLE AND NERVE FINDINGS AS RECORDED IN LITERATURE

To gain a more comprehensive picture of the various findings in the muscles and the nervous system in this condition, so far as known, it is necessary briefly to review the literature on this subject.

In Spiller's case the muscles amid a hypertrophic interfibrillary and fatty tissue were little developed; the fibers were hyaline and very small; their longitudinal striation was indistinct, the number of the nuclei of the connective tissue considerably increased. The nervous system was intact.

Bing observed in a very small piece of muscle, excised from a 3½ year old child, only a certain increase of the number of the nuclei.

Skoog noted a great diminution in the size of all muscle fibers, their diameters measuring from 8 to 12 microns; their myoplasma in many

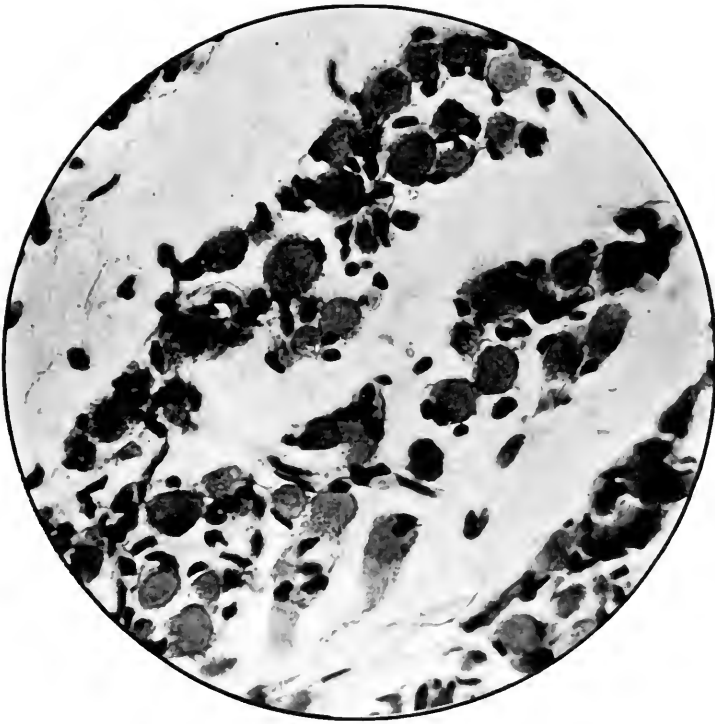


Fig. 3.—Atrophic muscle fibers of various diameter; fibers separated by proliferation of connective and fatty tissue. From microphotograph,  $\times 450$ .

places had undergone a complete degeneration and replacement with adipose or connective tissue. There was, moreover, much fatty tissue between the individual bundles, a very marked proliferation of the sarcolemma nuclei and a pronounced thickening of the walls of the vessels, including the capillaries.

While in these cases, including my own, only atrophic fibers were found, other authors, as Reyher-Helmholz and Collier-Holmes have observed, in addition, hypertrophic fibers in such numbers that the

microscopic pictures resembled more the ordinary findings of progressive muscular dystrophy.

Reyher-Helmholz noted that some of the muscles of their patient, especially those of the lower extremities, were much affected. The fibers—of which some were slender, some hypertrophied—were scanty and interrupted by adipose and connective tissue which abounded in nuclei; also the transverse striation was indistinct or entirely absent. Unfortunately the central nervous system was not examined to

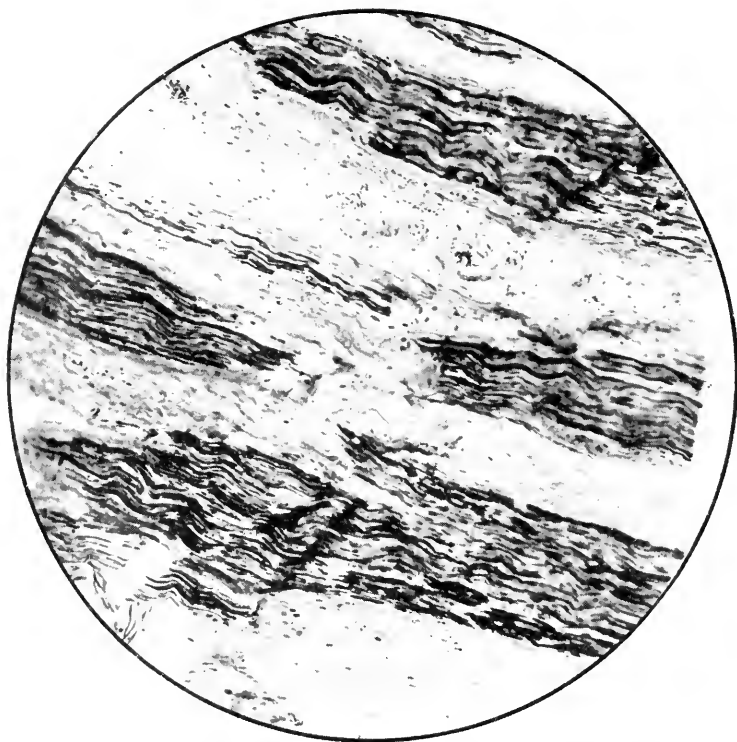


Fig. 4.—Peripheral nerve, stained by Weigert's method. Marked increase of fibrous connective tissue between the nerve bundles. From microphotograph,  $\times 65$ .

determine whether these changes were primary in the muscles themselves or secondary to an affection of the anterior horns of the spinal cord.

Collier-Holmes, having excised a piece of the hamstring muscle (in Case 2) under general anesthesia, noted that macroscopically it was markedly pale and very much infiltrated by fat tissue. Microscopically only a few fiber bundles were found to be normal; a great number of the fibers were extremely small, with an average diameter



of from 6 to 12 microns; their contour was irregular, being principally oval or round, and never presenting the normal polygonal or faceted appearance of cross-sections. These small fibers, when cut longitudinally, however, appeared of fairly uniform caliber and had a well-preserved cross striation. In some of these there was marked proliferation of the sarcolemma nuclei. Very striking indeed was the presence of numerous enormous fibers with diameters of from 100 to 150 microns. These giant fibers here and there presented regressive changes; some of them contained central nuclei either embedded in normal myoplasma or surrounded by a zone of undifferentiated sarcoplasma. In other fibers the regressive changes had led to vacuolization and a splitting up, or the more or less disintegrated myoplasma was invaded by the sarcoplasm and sarcoplastic nuclei. The connective tissue was greatly increased and in places even penetrated between the individual muscle fibers. There was also a notable amount of loose adipose tissue between the muscle bundles. The muscle spindles on the whole proved to be normal, but in places their sheaths appeared slightly thickened. Considerable thickening of the walls of many blood vessels was noticeable. In the muscles were remarkably few myelinated nerves and the myelin sheaths seemed poorly developed. In Case 1 (complete necropsy) the muscles presented lesions similar to those just described.

The myelin sheaths of the peripheral nerves were imperfectly developed, the ventral spinal roots were slender, the number of their fibers reduced and the myelin defective. The great motor ganglion cells of the anterior horns were reduced in number and size and were abnormally angular and irregular in shape.

Baudouin also has described hypertrophic in addition to atrophic fibers, proliferation of the connective tissue, multiplication of sarcoplasma nuclei and indistinct transverse striation. These changes, however, were of minor degree. The nervous system revealed profound alterations. The size and perhaps also the number of the cells of the anterior horns, was diminished; in the various nerve trunks many axis-cylinders were without myelin; the nuclei of the sixth and twelfth cranial nerves showed chromatolysis. Baudouin ascribed the condition to a retarded myelination of the nerves and an inhibition of the development of the cells of the anterior horns.

Rothmann's case presented even more extreme lesions. In addition to extensive atrophy of the great motor cells throughout the anterior horns of the cord were also alterations of the white substance and a diminution in number of the cells of Clark's columns. The smallness of the cord was striking. The motor ganglion cells of the hypoglossus nucleus were numerically decreased and showed chromatolysis. The

peripheral nerves were partly thickened, owing to enlarged septa of connective tissue, with multiplication of the nuclei. The transverse diameters of the nerve filaments were reduced, the single fibers were also very slender, though not changed in number or structure, and pursued a wavy course. The principal changes in the muscles consisted in pronounced proliferation of the intermuscular connective tissue, in abundant small cellular proliferation and marked development of fatty tissue between the muscle fibers, which last had partly disappeared.

Likewise Kaunheimer at postmortem in his case found, in addition to muscular changes, profound alterations of the nervous system. There were signs of severe degeneration of the peripheral nerves: marked diminution in number of the fibers, corresponding proliferation of the perineural and endoneural connective tissue and a marked increase of Schwann's nuclei. Many of the remaining fibers were small and of varying diameter; some showed a wavy course in longitudinal cuts. In various places the myelin sheaths and the axis cylinders were absent, though no marrowless axis cylinders could be detected.

The central nervous system showed extensive alterations, most pronounced in the motor cell columns of the spinal cord and in the medulla oblongata. There was proliferation of the glia in the marrow of the brain hemispheres, in the medulla oblongata and in the white substance of the spinal cord; atrophy in the nucleus of the hypoglossus nerve, in Clark's columns and the anterior horns of the entire spinal cord.

#### NATURE OF THE DISEASE

The views concerning the nature of the disease vary, inasmuch as many difficulties arise in the interpretation of the various pathologic changes.

Before any pathologic examinations were on record, Oppenheim regarded the disease as a retardation of development of the muscles, a conclusion later supported by Spiller, who failed to discover either gross or minute changes in the nervous system. Oppenheim, however, considered also the possibility of retarded development of certain nerve centers and their function, especially of the anterior horns of the spinal cord.

The findings of subsequent authors demonstrated indeed that the whole peripheral neuron may be affected, different segments varying in degree in different cases. If we remember that the ganglia cells of the spinal cord, the peripheral nerves and the muscle constitute a physiologic unit, this is not surprising.

The muscle findings place the affection near the group of the so-called primary myopathias—*dystrophia musculorum progressiva*. But while in myatonia the lesions extend to the nervous system in the majority of cases so far reported and are only exceptionally limited to the muscles, on the contrary, in dystrophy we observe, as a rule, muscular alterations alone, such as atrophy, hypertrophy of the fibers, multiplication of the muscle nuclei, etc., though in exceptional cases—those of long duration especially—degenerative alterations of the nerve elements were also found, these perhaps being secondary. (Transitional cases of Heubner, Struempell, Preis.)

On the other hand, since in primary spinal atrophies combinations with pseudohypertrophy of muscles also are known, the anatomic demarcation between myelopathic (spinal) and myopathic atrophies becomes still less sharp; though it must be admitted, that the hypertrophic fibers observed for instance in poliomyelitis acuta or in neurotic muscular atrophy were apparently present only in small number. All this tends to demonstrate the possibility of a relationship between primary dystrophy and spinal muscular atrophy.

A number of authors hold myatonia as at least a process closely related to muscular dystrophy, if not a congenital form of this disease. Jendrassik thinks that the possibility of improvement in myatonia as opposed to dystrophy forms no essential difference in the nature of these affections; for he considers in myatonia the clinical improvement not to be a real (anatomic) restoration but rather an improvement of the innervation of individual muscles or muscle fibers originally less affected. At present clinical evidence does not permit us to classify myatonia as progressive *dystrophia musculorum*. Also the frequency and degree of peripheral nerve and spinal cord alterations in myatonia evidence dissimilarity from dystrophy, and suggest a relationship to the spinal atrophies.

The possibility of the existence of primary lesions in the muscles in at least a number of cases will not be denied in the presence of such findings as Spiller reports though indeed the theory is permissible that in such cases the original minor affection of the motor ganglia cells was not irreparable, and for this reason the ganglia cells in the later stage of the process failed to show the former lesions. On the other hand, such a degree of lesions of the nervous system as quoted above seems almost to exclude the probability of anatomic restitution; and in view of my own findings I am inclined to attribute the clinical improvement in my case more to amelioration of the function than to a progressive anatomic development.

Rothmann calls attention to the great similarity of his findings in myatonia to those of Wernig-Hoffmann's spinal infantile atrophy of

the muscles, and also emphasizes that the clinical differences are not always marked, as cases of Wernig-Hoffmann's atrophy without family grouping are known, and, on the other hand, myatonia has been found among several members of the same family. (Sevestre, Collier-Wilson, Sorgente). Rothmann unites both forms in one group of spinal atrophies in spite of the clinical fact that myatonia is congenital and not progressive (with rare exceptions), whilst Wernig-Hoffmann's atrophy usually begins in the second or third semester of life. He thus distinguishes a congenital and an early infantile form which show no sharp line of demarcation. In his opinion, improvement in cases indicates that they should be regarded as of myatonia, while progressive cases belong to the Wernig-Hoffmann type of the disease.

He excludes fetal poliomyelitis in his case. Marchi specimens proved to him the fetal origin of the disease and that the degenerative processes were continued during the first months of life. He considers that agenesis of the ganglion cells is improbable.

As to the assumption that the disease shows a relationship to Moebius' infantile *Kernschwund* no verdict can be given at present; theoretically the possibility must be admitted that an affection does exist in which the cells of the anterior horns are aplastic or defective, a condition of similar nature to that shown in Moebius' *Kernschwund*; so that their function is either absent or is only present after a period of inactivity.

A resistentia minor of the protonuron may be possible in all these affections owing to developmental inferiority, which is only temporary in some cases and to a certain extent reparable (myatonia), but which in others is progressive and lethal (spinal muscular atrophy).

Kaunheimer concludes from the histologic examination in his case that myatonia must be considered as either a toxic or endogenic affection; the theory that the pathologic basis of this disease lies in inhibition of development or inflammatory processes should be discarded. The process is not necessarily complete at birth, as alterations of the muscles may result even months later.

Berti suggested from his study of his own and other reported cases that a relationship exists between myatonia and subcretinism or submyxedema; and Cattaneo and Silvestri likewise believe the disease to be due to a disturbance of some internal secretion. The sclerotic changes of the thymus noted by Spiller-Smith and the sclerosis of the spleen, thyroid gland and thymus observed in Baudouin's case seemed to support these views. In Rothmann's case the thymus was enlarged, Hassal's corpuscles being strongly developed; though he did not regard this as important. Other authors, as Collier-Holmes, Lereboullet-Baudouin and Rothmann could find no changes in these organs, so that

these isolated positive findings hardly offer a sufficient basis for broad conclusions. The improvement which occurred in Silvestri's case on adrenalin administration and in Lepine's case after thyroid therapy, may have been accidental since Oppenheim's disease has a tendency toward spontaneous improvement.

Though our experience concerning the function of the thymus so far does not establish its relationship to the muscle and nervous lesions seen in Oppenheim's disease, we know, nevertheless, that thymectomy in animals causes myasthenia with certain neuromuscular alterations in addition to the well-known skeletal changes. These are, simple atrophy with transition to degenerative atrophy in the muscles, marked reduction in the caliber of the fibers, partial loss of the transverse striation, multiplication of the sarcolemmal nuclei and the nuclei of the internal perimysium, and distinct proliferation of the interfascicular connective tissue with formation of adipose tissue.

These results of animal experiments possess interest also in connection with the muscular lesions in man, found in myasthenia gravis and myasthenia pseudoparalytica with persistence of the thymus, and in connection with the degenerative changes of the muscles seen in disturbances of various other endocrine glands, as in Basedow's disease.

According to Biedl examination of the nervous system of thymectomized animals revealed only minor alterations in the peripheral nerves and slight degenerative conditions in the spinal cord. The myelin sheaths in the cord showed disintegration, the ganglion cells of the gray matter were swollen, lighter stained, with indistinct protoplasm and changes of the nuclei, indicating also a beginning disintegration in them. These observations although for our problem merely suggestive and of only speculative service, should induce us nevertheless to direct careful attention to the organs of internal secretion at necropsies in future in cases of Oppenheim's disease.

At present the morbid agent in the spinal and muscular changes, the cause of Oppenheim's myatonia in the fetus is not known, nor do the findings allow an undisputed classification of the disease.

#### MUSCULAR LESIONS IN RACHITIC MYOPATHY

It may not be amiss to call attention here to affections of the muscular system demonstrated in such general diseases as rachitis. This rachitic myopathy is considered a primary, specific and co-ordinate to the alterations of the skeleton; it bears a certain clinical resemblance to myatonia congenita. The morphologic changes found in the texture of the muscles in the clinically pronounced hypotonia and pseudoparesis of rachitic babies were marked reduction of the caliber of the

fibers, defective transversal striation, marked longitudinal striation, striking increase in the number of the muscle nuclei, lack of fatty tissue, indistinct sarcolemmal edges and densely crowded fibers, conditions different from those seen in Oppenheim's disease.

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## A CASE OF CONGENITAL HEART DISEASE WITH DEMONSTRATION OF SPECIMEN \*

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Eli S. was born at full term, after a normal delivery, about Jan. 1, 1906. He weighed 3 pounds. His mother noticed, when he was 4 months old, that his lips, cheeks and nails were always blue and that at times he was blue all over. He was feeble from the beginning and, when he was old enough to exert himself, showed dyspnea on exertion. He had scarlet fever when he was 2 and whooping-cough when he was 3 years old. He was brought to the Children's Hospital for the first time Dec. 1, 1909, when he was about 4 years old. At that time he was small, but well nourished. His lips and nails were very blue and the mucous membrane of the mouth was cyanotic. There was marked, general cyanosis when he cried. There was marked clubbing of the fingers and toes and some bulging of the precordia. The heart was somewhat enlarged in both directions, and a very faint murmur was heard at the junction of the sternum and the third and fourth ribs on the left. There was also a very slight systolic murmur in the pulmonic area. These observations were made by a house officer, however, so that there is some question as to their accuracy. The patient was seen and examined repeatedly by various members of the visiting staff from that time until his final illness and no murmurs were ever heard by any of them. He developed well, was active and showed no evidences of discomfort referable to his heart. He was generally cyanotic, and the clubbing of the fingers and toes became extreme. The conjunctivae were discolored. There was no enlargement of the liver or spleen.

The blood showed from 120 per cent. to 140 per cent. of hemoglobin by the Sahli apparatus. The red corpuscles varied between 7,800,000 and 13,675,000, most of the time being between 11,000,000 and 12,000,000. The white count varied between 8,000 and 12,000. The differential count of the white cells showed on the average 32 per cent. of mononuclears and 68 per cent. of polymuclear neutrophils. There were never any abnormalities in the red cells.

The urine was normal at repeated examinations.

Aug. 9, 1914, when a little more than 8½ years old, the patient had an acute attack in which he vomited blood and passed blood in the stools. He was brought into the hospital in collapse, but had no recurrence of the hemorrhages. The urine contained albumin, casts, and a little microscopic blood. It was clear in about a month. The heart at that time measured 4 by 9.5 cm. There were no murmurs. The liver was 1 cm. below the costal border. The spleen was not palpable. The blood showed a white count of 33,800 at that time.

Subjective symptoms developed for the first time in early November, 1914. The patient was able to walk, but any greater exertion caused cardiac distress. He was unable to attend school or play. He complained of pain in the right chest. The cardiac measurements were 4 by 9 cm. There were no murmurs. The liver was 1 cm. below the costal border. The spleen was not palpable. He was examined at this time by Dr. L. E. Holt, who also heard no murmur.

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\* Read at the Annual Meeting of the American Pediatric Society, Lakewood, N. J., May 25-27, 1915. From the Children's Hospital, Boston.

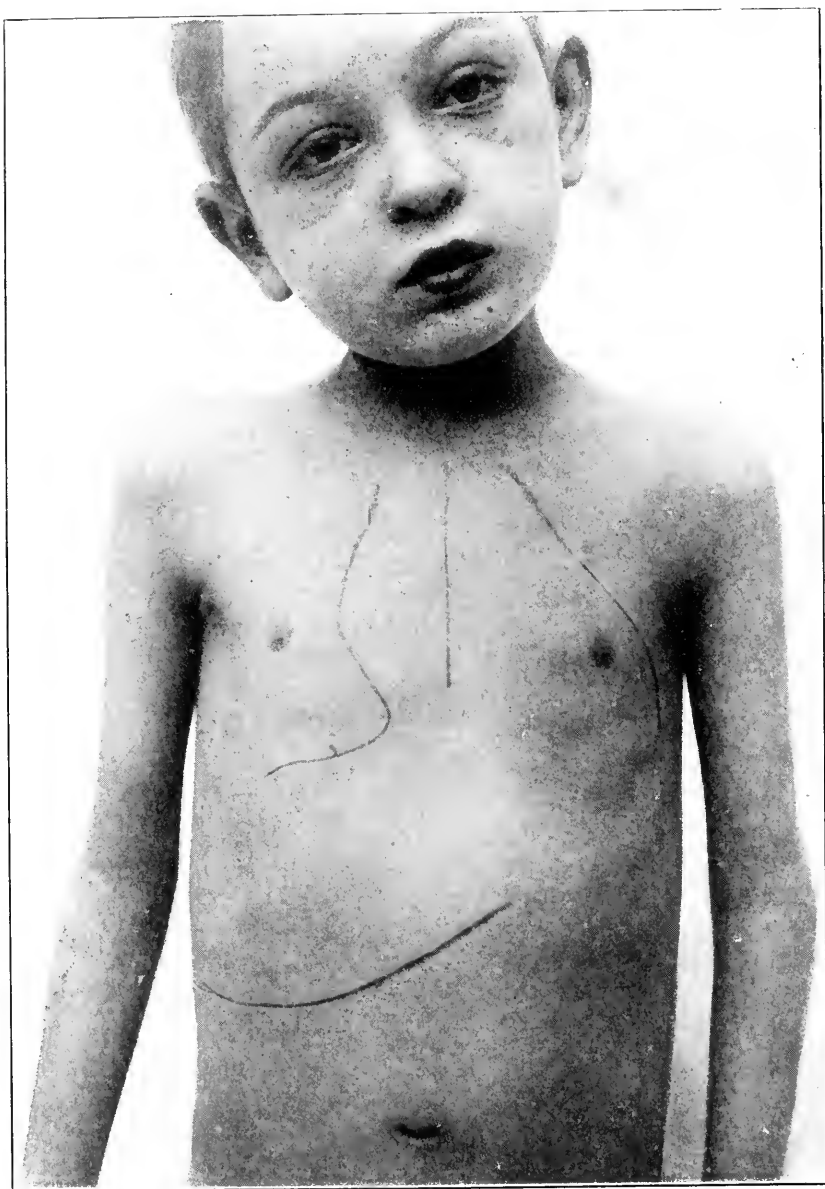


Fig. 1.—Patient with congenital heart lesion.



The patient stayed in the hospital only a few days at this time, but returned Nov. 30, 1914, with the story that he had been perfectly well until the night before, when he began to have constant and severe pain in the abdomen, with high fever and vomiting. The cyanosis was greater at this time than ever before and the temperature was 103 F. The condition of the heart was the same, except that it extended 10 cm. to the left. The urine was full of normal blood and also contained bile. The patient became slightly jaundiced during the next few days. He quickly improved, however, so that on December 4 the urine was normal. He was examined carefully December 2 by myself and several other men, including Dr. H. A. Christian. There were no murmurs

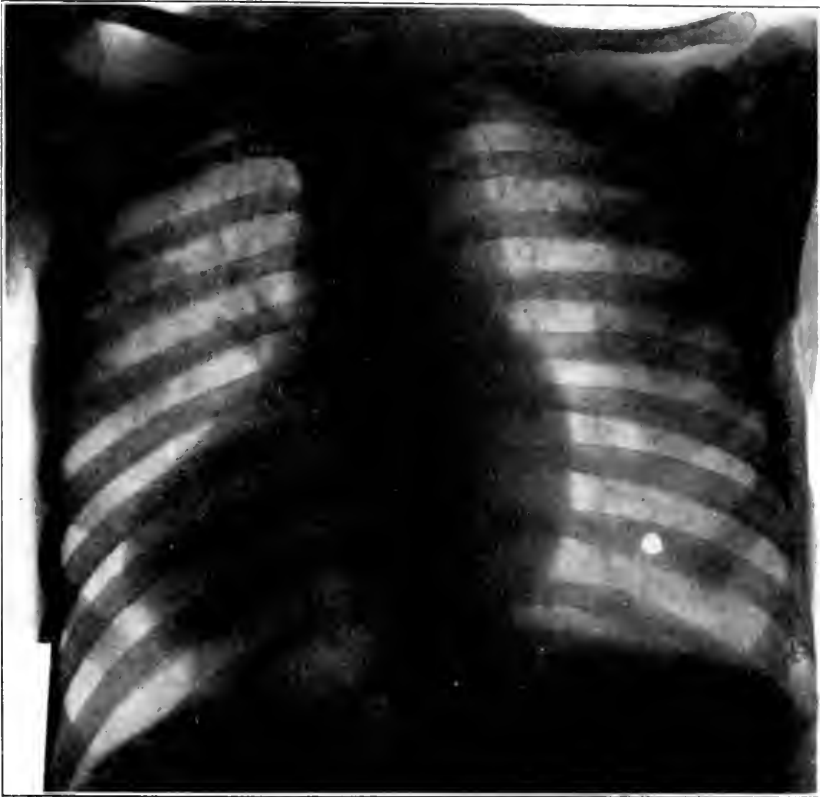


Fig. 2.—Heart as shown by Roentgen ray.

in the heart and there was no palpable thrill. The temperature had in the meantime dropped to normal in the morning, with an evening rise to 100 or 101 F.

He was not examined December 3. December 4, a diastolic murmur was present over the whole precordia, loudest in the pulmonic area.

The examination of the heart, Dec. 7, 1914, was as follows: The right border of the heart was 4.5 cm. to the right of the median line, and the left border 11 cm. to the left of the median line. The upper border was at the lower border of the second rib. The action was regular. There was a high-pitched murmur beginning just before the first sound, accompanying the first sound and continuing a little after it. The second sound was accompanied by a long, somewhat rough murmur, which was loudest in the third left space. It

was louder in the pulmonic area than in the aortic area or at the apex. The second sound was distinct. Figures 1 and 2 show the conditions at that time.

The measurements of the heart on the roentgenogram (Fig. 2) are as follows: Right border: first space 3 cm.; second space 4 cm.; third space 4.5 cm.; fourth space 2.5 cm. Left border: first space 3.5 cm.; second space 7 cm.; third space 11 cm.; fourth space 11.75 cm.

At this time the cyanosis was somewhat less than it had been in the past. There was no edema or ascites. The liver was palpable 3.5 cm. below the costal

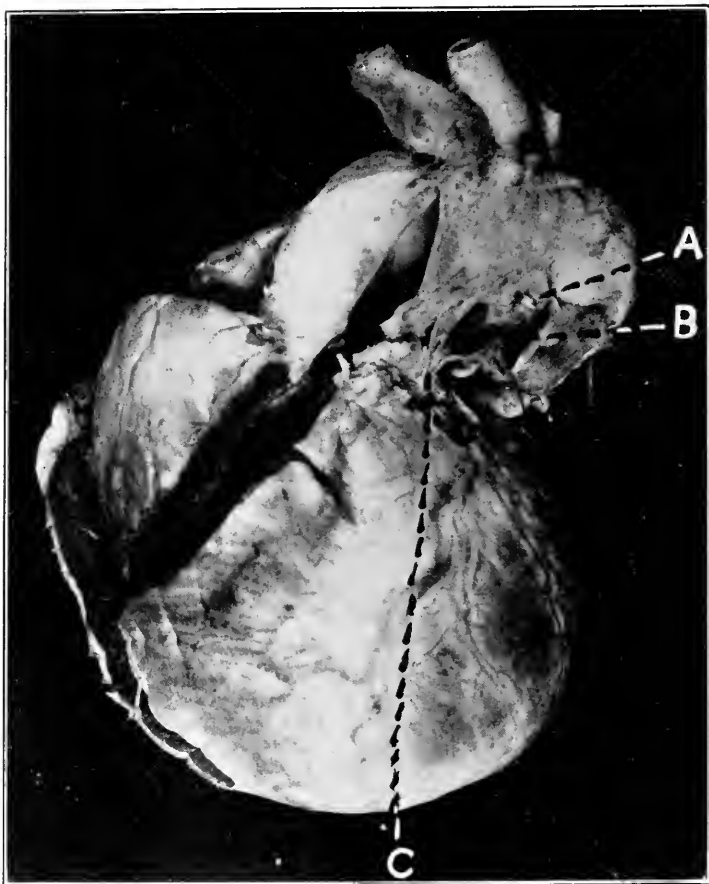


Fig. 3.—View of heart showing *A*, ductus arteriosus, *B*, two vessels to lungs, and *C*, rudimentary pulmonary artery.

border in the nipple line. The spleen was not palpable. The hemoglobin came down to between 100 per cent. and 115 per cent. by the Sahli apparatus. The red corpuscles ranged between nine and eleven millions and the white corpuscles between 9,000 and 10,000. The blood pressure, by the Tycos apparatus, was 120 in systole and 50 in diastole, giving a pulse pressure of 70.

The temperature rose again after the appearance of the murmur, but after a week dropped to normal in the morning with an evening exacerbation to from 100 to 101 F. By the middle of January the systolic murmur had almost disappeared and the diastolic murmur had become much fainter. The general condition continued unchanged, as did the condition of the heart. The patient died suddenly Feb. 10, 1915, presumably as the result of an embolus.

A positive diagnosis of congenital heart disease was made when he was first seen. The malformations with which the symptoms were reasonably consistent were absence of the ventricular septum, transposition or irregular origin of the great vessels and pulmonary atresia with some secondary malformation. There ought not to have been any second pulmonic sound, however, if there was pulmonic atresia, and it should have been accentuated if there was simply a transposition of the vessels. The most reasonable diagnosis, therefore, seemed to be absence of the ventricular septum. A single vessel coming from a single ventricle had been mentioned but had not been seriously considered.

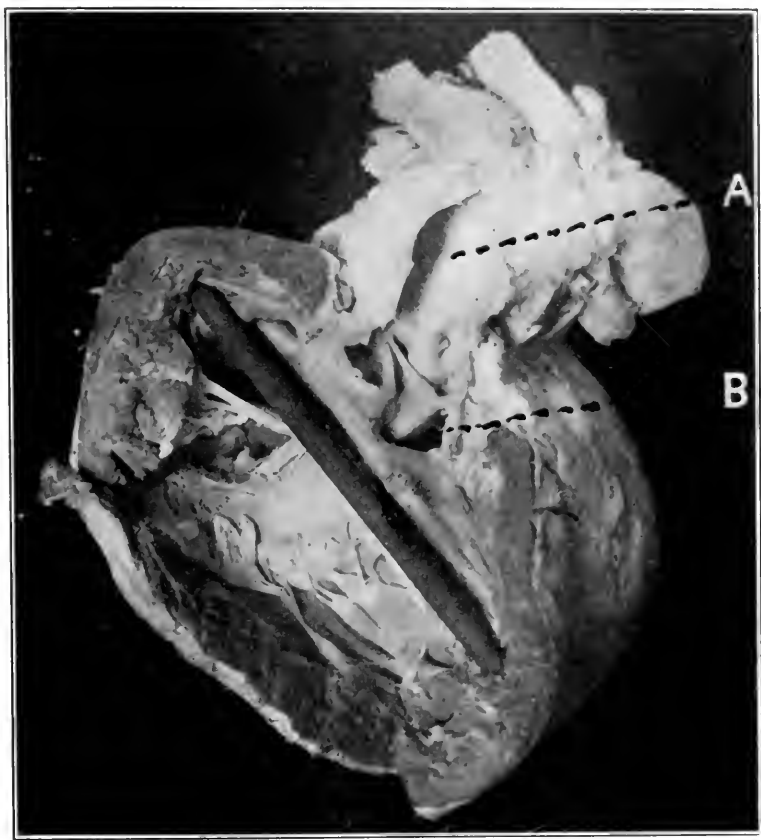


Fig. 4.—Heart cut open, showing *A*, single artery and *B*, opening between ventricles.

Unfortunately, it was possible to obtain only a partial necropsy. The heart and lungs alone were examined. The results of the examination by Dr. S. Burt Wolbach are as follows:

Gross anatomical diagnosis:

1. Complete congenital atresia of pulmonary artery.
2. Congenital defect of interventricular septum.
3. Persistent ductus arteriosus.
4. Acute vegetative endocarditis.
5. Thrombosis of ductus arteriosus.
6. Patent foramen ovale.
7. Dilatation and hypertrophy of right ventricle.

The heart is greatly enlarged and weighs 130 gm. (normal, 105 gm.). The general shape is that of a normal heart, but the right border is rounded and it is evident that the right ventricle is enlarged. The auricles are in their normal position. The appendage of the left auricle, however, is narrow and projects as a curved process, 2.5 cm. long and 0.5 cm. broad.

There is a single arterial trunk which arises at the base of the ventricles anterior to the auricles. The tips of the right and left auricular appendages appear on their respective sides of this vessel. On opening the heart it is found that this vessel arises from both ventricles. Its orifice is directly above the interventricular septum, which is deficient. This deficiency corresponds to that resulting from the absence of the membranous portion of the septum. Its upper border is the attachment of the anterior segment of the mitral valve. Its right pillar extends to the base of the right anterior segment of the semilunar valve of the arterial trunk, while its left pillar extends to the junction of the left anterior and the posterior segment of the valve. The size of the interventricular opening is 2 by 1 cm. (after hardening). The arterial trunk is apparently effectively guarded by the semilunar valve, a posterior and a right and left anterior. The free edges of these segments are slightly thickened and covered with pale, grayish, friable granulations. The coronary arteries take their origin behind the posterior and the left anterior segments. The size and shapes of the segments are those of a normal aorta in a heart of this size. The circumference is 8 cm. The arch corresponds to the arch of the aorta and is continuous with the descending aorta. The vessels given off are in the order named; the innominate, left common carotid, a small thin-walled ascending vessel and a left subclavian. At the location of the ductus arteriosus a large vessel takes origin by a short trunk, which divides into a right and left pulmonary artery. From this trunk running down along the main arterial trunk, is a thin-walled, small calibered vessel, 2 to 3 mm. in diameter. This vessel ends blindly, gradually disappearing to a point in the myocardium between the posterior and left anterior segments of the valves of the main arterial trunk.

The orifice of the pulmonary trunk into the arch of the main arterial trunk is 0.4 cm. in diameter, and nearly wholly occluded by a firm, grayish-red clot. This clot is cylindrical in shape, 0.4 cm. long, and attached firmly over one-half its circumference (organized).

The mitral and tricuspid valves are normal in appearance. The mitral measures 8.5 cm. in circumference at the attachments of the segments, and the tricuspid valve measures 10 cm.

The venous orifices in the auricles are normal in number and position. The foramen ovale is patent by an oblique passage.

The endocardium is normal, except for the aortic changes noted and a few minute vegetations on the inferior border of the opening between the two ventricles.

The myocardium is firm, of normal color and consistency. The left ventricular wall averages 1 cm. in thickness; the right is 0.9 cm.

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## ACUTE INFECTIVE ENDOCARDITIS

DUE TO STREPTOCOCCUS ATTENUANS IN A CHILD ONE YEAR OLD \*

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Acute endocarditis, simple or malignant, is (with rare exceptions) a secondary and not a primary process. The morbid condition is the result of an infection by some micro-organism or its toxin. The action, Anders believes, is assisted by the friction between the blood current and the surfaces of the valves. The pathologic processes, though identical in nature, differ in degree and severity in the so-called simple, the intermediate grades and the more rapidly fatal or ulcerative type.

A good working classification, either etiological, anatomical, or clinical, is not easy to make. According to the *nature of the infecting agent* we speak of streptococcic, staphylococcic, pneumococcic, rheumatic, typhoid or gonococcic; according to the *character of the lesion*, of verrucose or ulcerative; according to the *severity of the symptoms*, of benign and malignant varieties.<sup>1</sup>

Lamb and Paton<sup>2</sup> report a case of vegetative endocarditis caused by a heretofore undescribed spirillum (*Spirillum surati*).

Dean recorded an example of generalized actinomycotic infection in which the endocardium was implicated. The elaborate and thorough work of E. Libman in particular, has given us valuable information regarding the cases of subacute infective endocarditis.

The most frequent cause is acute articular rheumatism, comprising about 10 per cent. of the acute cases. In lobar pneumonia Osler found it in eleven out of twenty-three cases. Septic conditions may also act as a cause. It has occurred in measles, tonsillitis, scarlet fever, typhoid, erysipelas, chorea, tuberculosis, etc.

The protean aspects of the disease are influenced or rather due to the specific character of the infecting organism. The manifestations may be those of septicopyemia, in which chills, fever, hemorrhages, septic emboli, etc., are due to suppurative lesions. Or in the non-suppurative forms, the picture is that of a septicemia with high and irregular temperatures. The symptoms are so diverse that in many cases it is impossible to differentiate the suppurative from the non-suppurative.

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\* Read by title at the Annual Meeting of the American Pediatric Society, Lakewood, N. J., May 25-27, 1915.

1. Osler: Modern Medicine, 1908, iv, 133.

2. Lamb, Albert R., and Paton, F. Wade: THE ARCHIVES INT. MED., Sept., 1913, p. 259.

tive varieties. Not infrequently, when cerebral symptoms predominate, a lumbar puncture is advisable in order to exclude a possible meningitis. The cardiac symptoms vary. We may have extensive involvement of the valves with negative physical signs on auscultation. In other cases, more or less distinct murmurs, depending on the valves involved, may be discovered. As E. Libman remarks, "the absolute diagnosis rests on the cultural study of the blood."

In arriving at a diagnosis it is of the utmost importance to study the previous history and conditions under which the individual case occurs. With the symptoms referred to above and the evidences of emboli, petechiae, etc., a diagnosis is possible, even though cardiac murmurs are absent. Blood cultures, however, are necessary in order to establish the identity of the organism, the specific cause of the disease under consideration.

Streptococcic endocarditis is of frequent occurrence in adults. To judge from the literature it is extremely rare in patients as young as the following.

#### REPORT OF CASE

Rachel S., 1 year old, born in New York, was admitted to the children's ward (service of Dr. A. F. Hess) Dec. 20, 1914.

*Family History.*—Father and mother living and well. Two brothers and one sister alive and in good health. No history of any hereditary disease could be elicited.

*Previous History.*—The child was born at full term, delivery normal. Breast fed at the beginning, now receives milk three-fourths and water one-fourth; also other food from the table. No vomiting, convulsions or nervous symptoms reported. Appetite good, bowels regular.

The present illness began about four days before admission (although the child had been coughing for the past four weeks) with convulsions, dyspnea and cyanosis lasting about fifteen minutes. These symptoms subsided after an enema had been given. The child had another convulsion similar to the first, several hours subsequently, again two days ago and on the morning of day when sent to the hospital. The patient was constipated; a laxative was given, resulting in foul smelling greenish stools. There was no vomiting. Occasional cough was noticed; there was some dyspnea. Fever was marked. Since the onset of the trouble the child had been drowsy and very irritable.

On admission temperature was 101, pulse 146, respiration 40. General condition: Patient fairly well developed and nourished, slight dyspnea and cyanosis noted, no prostration or edema observed.

Eyes: Pupils equal, regular and react to light and accommodation. Petechiae present in conjunctival mucous membranes.

Nose, ears and mastoids presented no abnormalities.

Tongue clear and moist; pharynx and tonsils congested. No rigidity of neck; nasal, throat and vaginal smears negative.

In the lungs, with the exception of harsh respiratory murmur in right infra-clavicular space and right axilla, the signs were negative.

The heart was not enlarged; a soft blowing murmur transmitted to the left and heard in the axilla was evident on examination. The second pulmonic was not accentuated.

The pulse was rapid, without any irregularity or intermission.

The abdomen was somewhat tympanitic, no tenderness or rigidity present. Liver was not palpable. Spleen was enlarged and could be readily felt about one finger below costal margin. The skin was hot and dry; glands not palpable, no rash present on the integument. Knee jerks active, no Babinski present.

## BLOOD EXAMINATIONS

Date .....	12/21/14	12/23/14	12/27/14	1/2/15
Number .....	4,200,000	.....	.....	3,100,000
Hemoglobin .....	75%	.....	.....	65%
White Blood Cells.....	27,000	24,000	20,000	26,000
Small Mononuclear .....	48%	.....	.....	.....
Large Mononuclear .....	6%	27%	36%	30%
Transitional .....	1%	1%	.....	.....
Polynuclear .....	45%	72%	64%	70%

Urine: Dec. 22, 1914: Straw color, acid, faint trace albumin, no sugar, acetone or diacetic acid—no bile, blood or pus. Same result when examined three days later.

Roentgenoscopy of joints and chest negative.

Dec. 28, 1914: Ears examined by Dr. Wolff Freudenthal; both drums normal.

Dec. 29, 1914: Blood culture revealed *Streptococcus attenuans*.

*Bacteriologic Report by Dr. J. J. Hertz, Bacteriologist to Beth Israel Hospital.*—Five c.c. of blood was obtained from the vein at the elbow, and divided in equal parts into two flasks, one containing 100 c.c. of 2 per cent. glucose bouillon and the other 100 plain bouillon. At the end of twenty-four hours the plain bouillon showed no growth. The glucose bouillon showed a streptococcic growth in chains of two to seven cocci. The organism was plated on blood agar plates and the colonies showed hemolysis. At the end of five days, the plain bouillon showed no growth.

January 1 with the change in the service, the patient was transferred to me. I take this opportunity to extend thanks for the courtesy of the case to Dr. Hess, attending physician.

Child well developed and nourished, was pallid, extremely irritable and restless, so that a thorough examination of lungs was not feasible. A distinct systolic murmur propagated to the left, was heard over the precordial region. Heart slightly enlarged, impulse fair. Spleen distinctly to be felt. Liver apparently normal; no jaundice present. Eyes somewhat sunken with dark circles underneath, face dirty waxy color. Tenderness over lower part of sternum, on which E. Libman lays stress, could not be elicited because of apathetic condition of patient.

This morning the child developed large patches of hemorrhagic spots about 2 cm. in diameter, over both cheeks and upper part of left chest. In addition small spots over right side of forehead. The rapid appearance of the patches on the cheeks led the parents to imagine that the child had been slapped and abused. It was with the greatest difficulty that the father was convinced of the falsity of any such assumption.

Jan. 2, 1915: Punctate hemorrhages under left eyelid noticed this forenoon. Weakness progressive. Color more dusky; apathy more pronounced.

Jan. 3, 1915: Bloody stools and vomitus to-day; child failing.

Jan. 4, 1915: Progressively growing weaker; respiration more rapid; pulse rapid and irregular; color more sallow, anemia more marked; died of cardiac failure about 6 a. m.

*Necropsy Report by Dr. Eli Morchowitz, Pathologist.*—Lungs: Do not collapse. Pleura covered by numerous petechiae. Both lungs feel solid, only portions of upper lung are crepitant. On section lungs are salmon pink in color, firm, consolidated and fleshy in appearance. Bronchial nodes are not enlarged. Slight edema of both lungs.

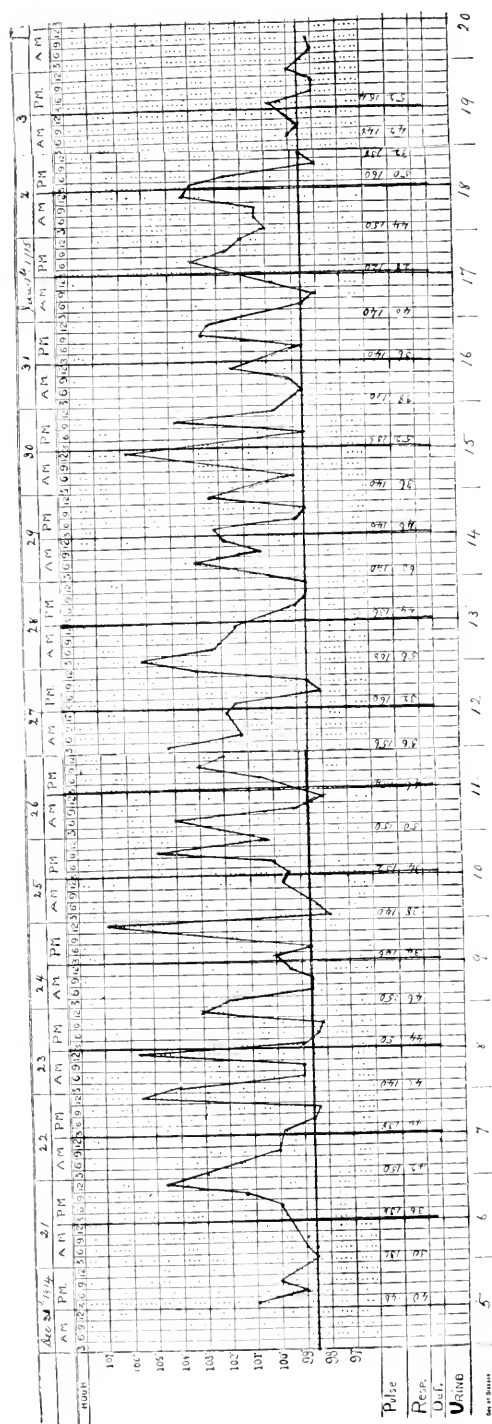


Fig. 1.—Temperature chart.



**Heart:** Slightly enlarged. Left ventricle moderately dilated and slightly hypertrophied. The auricular surfaces of mitral flaps are covered by numerous firm verrucous-like vegetations, the largest projections being close to edges of valves. These vegetations are more extensive on the posterior flap where they extend upward on the auricular wall almost to opening of pulmonary vein. The vegetations are in part covered by a thin layer of fresh fibrin. In the neighborhood of the vegetations are a number of ecchymoses on the endocardium. The other valves of the heart are normal. Muscle slightly flabby and pale red.

**Liver:** Greatly enlarged; surface smooth. On section it is intensely cloudy, markings being very much obscured.

**Gall Bladder:** Contains green bile. Otherwise normal.

**Spleen:** Slightly enlarged, capsule tense, surface smooth and firm. On section, the pulp was firm and purplish red, malpighian bodies distinct, trabeculae prominent. Pulp does not scrape. There are two small fresh white infarcts just beneath the capsule.

**Kidneys:** Normal in size. On section very cloudy, markings indistinct, bases of pyramids congested. Scattered over the surfaces of both kidneys are a few minute petechiae surrounded by a narrow pale zone which extends for a short distance into cortex. Capsule not adherent.

**Adrenals:** Normal.

**Intestines:** Normal.

**Mesenteric Lymph Nodes:** Not enlarged.

**Anatomic Diagnosis:** Acute verrucous endocarditis of mitral valves; slight edema of both lungs; pneumonia of heart disease (bilateral); hypertrophy and dilatation of left ventricle; cloudy swelling of heart muscle; cloudy swelling of liver; chronic congestion of spleen with fresh infarction; cloudy swelling and chronic congestion of kidneys with fresh infarctions.

**Microscopic Findings:** Lungs: Walls of alveoli are slightly thickened; the capillaries are dilated. The majority of the alveoli are either partially or completely filled by red blood cells, fibrin and large cells of endothelial type containing a small amount of pigment. The bronchi and pleurae are normal.

**Heart:** The striae of heart muscle cells are obscure, nuclei stain faintly. Otherwise normal. Heart valve mitral is covered by masses of necrosed fibrin in which are numerous clumps of bacteria. The entire valve has been converted into granulation tissue. There is an abundant round cell and polynuclear infiltration and formation of new blood vessels. The muscular wall of the heart adjacent to the valve is infiltrated with young connective tissue and formation of young blood vessels. This tissue separates the muscular bundles from one another.

**Liver:** Liver cells stain faintly, appear very granular, nuclei are pale. The liver cells contain a large number of fat globules. The capillaries around central veins are slightly dilated and the liver trabeculae in these regions are correspondingly narrower, the cells showing more pronounced granular and fatty degeneration.

**Stomach:** Normal.

**Spleen:** The splenic veins, especially in the cortex, are greatly dilated. The pulp is considerably congested. The center portions of the malpighian bodies stain lightly and consist of a delicate stroma of fine fibrillary connective tissue lined by large spindle cells of endothelial type.

**Kidney:** The epithelial cells of the tubules are coarsely granular; the cell outlines are indistinct, nuclei are sharply outlined. Most of the tubules contain a greater or less amount of granular material. The glomeruli are engorged with blood and the capillaries between the tubules are dilated and the capsule of Bowman reveal no changes. The infarcts are represented by a wedge shaped necrotic area in which the outlines of the tubules are distinctly visible. The

infarct is surrounded by a well defined narrow zone of young connective tissue proliferation. The lymph nodes of mesentery are slightly edematous.

Uterus: Normal.

The treatment is symptomatic and unsatisfactory. Antistreptococcic serum has proved efficacious in a few cases. Brodbent thinks the vaccine treatment affords some promise of success. Dr. R. Abrahams<sup>3</sup> reports the case of a girl 22 years of age, who recovered, after three injections of auto serum.

NOTE.—Since the above was reported, another case in a girl about 4 years of age came under observation in the Children's Service of Beth Israel Hospital. The patient was admitted for rheumatic endocarditis and on routine examination of the blood streptococcus alternans was found. The case will be reported in detail at a later date.

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3. Abrahams, R.: New York Med. Jour., Dec. 19, 1914.

## CATARRHAL JAUNDICE IN INFANCY \*

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Catarrhal jaundice, or acute duodenitis with icterus, is a common disease in children between the ages of 3 and 6 years. It is, however, only infrequently met in children under 2 years of age, and is extremely rare during the first year of life. Holt,<sup>1</sup> for example, states that he has never seen a case in a child under 2 years of age. Henoch,<sup>2</sup> the "father of pediatrics," saw only two cases in children under 1 year in all his wide experience, one of these being 8 weeks, the other 5 months old. Flesch,<sup>3</sup> writing from Bókay's clinic, classes catarrhal jaundice in infants under 1 year as among the greatest rarities, and in looking over the records of Bókay's "Stefanie Children's Hospital" for a period of ten years, found only one typical case (a baby 1 month old) among 160,000 admissions. Starck<sup>4</sup> reports 65 cases of icterus in children with none under one year. L. Nicolaysen<sup>5</sup> (Christiania) reports 49 cases of icterus in children, not one of whom was under 2 years of age. Skormin<sup>6</sup> (writing from Heubner's clinic) reports three cases, one of which occurred in a month old babe, one in an infant 14 days old, and the third in an infant only 4 days old. The last two children died, the former showing no hepatitis postmortem, but colon bacilli and a coccus in the liver and blood, and the latter (the 4 day infant) showing a duodenitis with hemorrhage into the brain and meninges. These appear to be doubtful cases at best. Neumann<sup>7</sup> reports 430 cases of catarrhal icterus in children, with 6 in the first year of life, and 70 in the second and third years together. Langer<sup>8</sup> reports 144 cases in children, with one in the first year, and 19 in the second and third together.

In view of the rarity of this condition, it seemed worth while to place the following three cases on record.

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\* Submitted for publication May 3, 1915.

\* From the Department of Pediatrics, Washington University, and the St. Louis Children's Hospital; read before the St. Louis Pediatric Society, March 19, 1915.

1. Holt, L. E.: Diseases of Infancy and Childhood.

2. Henoch: *Lehrbuch der Kinderheilkunde*, Ed. 9, p. 571.

3. Flesch, H.: *Jahrb. f. Kinderh.*, 1904, ix, 776.

4. Starck: *Jahrb. f. Kinderh.*, 1898, xlvii, 215.

5. Nicolaysen, L.: *Deutsch. med. Wchnschr.*, 1904, No. 24, p. 878.

6. Skormin, B.: *Jahrb. f. Kinderh.*, 1902, lvi, 176.

7. Neumann, H.: *Deutsch. med. Wchnschr.*, 1899, No. 35, p. 574.

8. Langer: *Prag. med. Wchnschr.*, 1905, No. 23.

CASE 1.—Baby John S., aged 8 months. Father and mother living and well. First child. No miscarriages or history of lues in family. Bottle fed baby (cow's milk formula) because of insufficient breast milk. Baby under observation from birth, has never shown any signs of lues, and, with the exception of a period of fat indigestion several months earlier, has always gained normally. Became ill Oct. 19, 1914, with increasing anorexia and drowsiness, which did not become alarming enough to suggest calling a physician until three days later. October 22, baby developed a temperature of 104, loose bowels, and increased somnolency. The next day the baby was distinctly jaundiced, and had six white, pasty, foul-smelling stools, with here and there small, black, tarry masses which gave a positive guaiac blood test. The urine showed bile. The white, pasty stools, from six to ten in number, persisted for three days, during which time the baby was intensely jaundiced and had fever up to 102-104 (rectal). The liver was enlarged and tender, and the spleen was palpable. Schmidt's test for bilirubin and urobilin in the feces was negative. October 26, the baby's temperature was normal; he was less jaundiced, and the feces were a light yellow in color. From this time on he made a rapid recovery, so that October 28, six days after the onset of severe symptoms, and nine days after the first sign of being ill, he was apparently well again. The spleen returned to normal with the drop in temperature, but the liver remained somewhat enlarged for several weeks longer. The only treatment was the substitution of skimmed milk for the whole milk formula.

CASE 2.—Baby Max S., aged 11½ months, was referred to the St. Louis Children's Hospital because of vomiting and diarrhea. Family history negative. Father and mother living and well, no history of lues or tuberculosis, the patient the youngest of a large family. On admission liver and spleen were not palpable, urine was negative, and von Pirquet and Wassermann were negative. Nov. 2, 1914, several weeks after admission, while the baby was apparently doing well, he developed jaundice, the skin and sclerae became yellow, and the urine showed bile. The stools became white and pasty. The liver was four fingers' breadth below the costal margin, and tender. November 1 he had four light yellow stools; November 2, the day on which jaundice was first noticed, he had three white pasty stools, November 3, one white stool, November 4, one light yellow stool, and thereafter a gradual return to normally colored feces. The temperature during this period ranged from 101 to 103, and there was distinct drowsiness. The jaundice cleared up as the stools regained their normal color, but he continued to run an irregular temperature. Three days later (November 6) the baby developed a cervical adenitis which went on to suppuration. November 13, the glands were incised, pus evacuated, and the temperature dropped to normal, where it remained.

CASE 3.—Baby Mary G., aged 2 months, admitted to the St. Louis Children's Hospital, June 2, 1914, with the complaint that she had "turned yellow" the week before. Father and mother living and well, no history of tuberculosis or miscarriages. The baby was the first child, and was born prematurely at 7 months, the birth weight being unknown. Never breast fed, but given condensed milk from birth. Had an otitis media at one month of age. Had a gonorrheal vaginitis on admission. One week before admission mother noticed that the baby was yellow, and this increased slightly down to the time of admission. Skin and sclerae were distinctly jaundiced. Urine was dark brown and contained bile. Mother said stools had been hard, white and constipated during the past week, but on admission were light yellow, watery, and two a day. Had had fever all week, the temperature before admission going to 104. No vomiting. When first ill, was put on a cow's milk formula. The heart and lungs were negative, the liver extended 3 cm. below the costal margin in the right mammary line, and the spleen was barely palpable. A week later, the jaundice had started to clear up; there was no more fever, the baby had gained slightly in weight, and was passing normal stools. From this time on the jaun-

dice rapidly cleared up and the liver became normal in size. This baby gave a positive Wassermann, but the course of the jaundice was typical of the catarrhal variety and there is little doubt but that it should be classed as such.

Just why this condition should be so rare in infancy seems hard to understand, for it is precisely at this age that children are most subject to gastro-enteric disorders, either through errors of diet, or through bacterial infection, two factors which are supposed to favor the occurrence of catarrhal jaundice. Perhaps, as Finkelstein<sup>9</sup> and others suggest, the explanation lies in the peculiarities of the infant diet; milk, as modified by the digestive juices, may become unsuitable for the multiplication of the specific bacteria or toxin necessary to produce the symptom complex under consideration. Until we know more of the etiology, however, this question can be answered only in theory.

Catarrhal jaundice in infancy differs very little from the familiar picture seen in older children. The causative factor is generally considered to be some infection, and indeed, epidemics of jaundice have been described by numerous observers. It may occur as a complication or sequel of one of the other infectious diseases, or, oftener, as a primary disease. There is usually a gastroduodenitis of varying degree, with swelling and obstruction of the common bile duct.

The attack usually begins with anorexia, coated tongue, abdominal pain of varying degree, vomiting, somnolency, slight prostration and fever. In infancy, the somnolency may be a marked feature, and there may or may not be diarrhea. Usually in two or three days, the characteristic jaundice of sclerae and skin makes its appearance, and the stools become gray or whitish, and greasy looking from the presence of unabsorbed fat. The stools are often quite foul in odor, and examination shows many fatty acid crystals. The urine is dark and shows the presence of bile. The liver is usually swollen and tender, and the spleen often enlarged. The pulse is usually slowed, sometimes markedly so, and may be irregular, but these features are ordinarily not prominent in infancy. Usually, after a few days the fever drops, the child feels better, and the jaundice disappears, but in the obstinate cases, jaundice may persist for several weeks. The liver ordinarily remains somewhat large for many days, or even weeks, after the jaundice has disappeared. The average duration of the acute symptoms, however, is from several days to two or three weeks.

The *prognosis* is almost invariably good.

The *treatment* consists mainly in dietetic measures, restricting the fats especially, and, to a lesser extent, the carbohydrates. Laxatives may be given, the salines being just as effective as the time-honored calomel. As improvement takes place, the diet may be gradually brought back to the normal.

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9. Finkelstein, H.: Lehrbuch d. Säuglingskrankheiten, Part III, p. 441.

# PROGRESS IN PEDIATRICS

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## REVIEW OF THE LITERATURE ON THE FEEDING AND GASTROINTESTINAL DISEASES OF INFANTS FOR THE YEAR 1914-1915 \*

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### BREAST FEEDING

1. Von Torday: *Jarb. f. Kinderh.* (ref.), 1914, lxxix, 373.
2. Pritchard: *Am. Med.*, 1914, xx, 327.
3. Misch: *Ztschr. f. Säuglingsschutz*, 1914, vi, 56.
4. Bahrdt: *Ztschr. f. Kinderh.*, 1914, x, 129.
5. Brodsky: *Arch. f. Kinderh.*, 1914, lxiii, 161.
6. Craige: *Jour. Am. Med. Assn.*, 1915, lxiv, 502.
7. Rietschel: *Ztschr. f. Geburtsh. u. Gynäk.*, 1914, lxxv, 732.
8. Jaschke: *Ztschr. f. Geburtsh. u. Gynäk.*, 1914, lxxv, 736.
9. Leo-Wolf: *Arch. Pediat.*, 1914, xxxi, 363.
10. Deresse: *Ztschr. f. Kinderh.* (ref.), 1914, viii, 508.
11. Hill and Simpson: *Proc. Soc. Exper. Biol. and Med.*, 1914, xi, 82.
12. Hill and Simpson: *Am. Jour. Physiol.*, 1914, xxxv, 361.
13. Editorial: *Jour. Am. Med. Assn.*, 1914, lxiii, 2292.
14. Myers: *Jour. Am. Med. Assn.*, 1914, lxiii, 1179.
15. Van der Bogert: *Arch. Pediat.*, 1915, xxxii, 35.
16. Neff: *Jour. Am. Med. Assn.*, 1914, lxiii, 1181.
17. Duke: Publication U. S. Children's Bureau, No. 9, Infant Mortality Series No. 3.
18. Hirsch: *Monatschr. f. Geburtsh. u. Gynäk.*, 1914, xxxix, 64.
19. Lateiner-Mayerhofer and Progulski: *Oester., Sanitätszw.*, 1914, xxvi, 1.
20. Rohmer: *Reichmed. Anzeiger*, 1914, xxxix, 225.
21. Churchill: *Jour. Am. Med. Assn.*, 1914, lxiii, 1799.

As in previous years, much has been written about breast feeding. While many authors have shown again by statistics the relation of breast feeding to a low infant death rate others consider this fact as well established, and are chiefly concerned with the practical difficulties presented by many cases of breast feeding.

### *Technic*

Von Torday<sup>1</sup> and Pritchard<sup>2</sup> emphasize the fact that the regular mechanical stimulation to the breast, caused by the sucking of the infant, is very important for a plentiful milk-supply. A regular routine in lactation is considered very important by Pritchard for establishing an automatism in milk secretion; nevertheless he believes that

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the longer interval at night should be used. He emphasizes the importance of the nervous element in milk secretion; and he believes the fact that the higher nervous centers have so undoubted an influence on milk secretion can be utilized therapeutically.

Misch<sup>3</sup> has found that it is impossible to maintain an abundant milk-supply for any length of time when the stimulation to the breasts is insufficient, as in cases in which the mother nurses her infant only three times daily. With four feedings daily better results are obtained.

Bahrdt<sup>4</sup> measured the amount of suction exerted by a nursing infant, with the object of discovering the reason why some infants nurse badly. He found that the suction necessary to obtain a flow of milk varied widely; that the normal infant could suit the suction exerted to what was necessary; and that infants who nursed badly exerted less pressure than was necessary. These children showed a failure to adapt the pressure to the breast.

Brodsky<sup>5</sup> has studied the amount of milk secreted daily by seventeen wet-nurses in whom the breasts were completely emptied after nursing. This method he recommends as tending to maintain the milk supply. The proportion of the milk removed to that nursed was 3.4 per cent. to 46 per cent. The average daily amount secreted by the wet nurses varied from 577 gm. for 77 days to 3,500 gm. for 339 days. The highest daily quantity was 5,400 gm.

The intervals between feedings generally recommended are three or four hours. Craige<sup>6</sup> recommends a three hour interval, with one night feeding until the third or fourth month, after which time all night feedings should be discontinued. Some babies, he believes, do better on four hour intervals. Overfeeding due to too frequent feeding he finds very common among breast-fed babies.

In feeding new-born infants, Rietschel<sup>7</sup> believes that the intervals should be shorter; he warns against the systematic method so often advised of feeding new-born infants only five times in twenty-four hours, for he finds that many of these children thrive better on six to eight feedings in twenty-four hours.

Jaschke<sup>8</sup> disagrees with this view, and advises even in new-born infants five feedings in the twenty-four hours. If the amount of milk taken is insufficient, he advises that the breasts should be pumped, and that this milk be given after each nursing.

Leo-Wolf<sup>9</sup> also recommends less frequent intervals of feeding for the new-born infant. On the first day the baby should not be nursed at all, and on the second day once or twice, while water *ad libitum* is given. The number of feedings is increased on the third day to three, on the fourth to four; and only on the fifth day is the infant to be nursed every four hours during the day.

Deresse<sup>10</sup> does not find insufficient amount of breast-milk to be the principal cause of inability of mothers to nurse their infants. Among one hundred mothers, in only twenty was the cause either insufficient amount of milk or disease.

All writers seem agreed that galactogogues have no influence in increasing the supply of breast milk. Hill and Simpson<sup>11</sup> have investigated the effect of the injection of the extract of hypophysis on the milk secretion of cows. This has been found by some writers to have a very marked effect. The authors found that there was a decided increase in milk secretion, with a rise in the percentage of fat. This was very temporary, and was present only in the first few hours after the injection; later the changes were counterbalanced, so that the examination of the daily amount showed no changes from the normal. They<sup>12, 13</sup> have lately made the experiment on the human subject, injecting 20 mg. of the commercial preparation intramuscularly. This was followed in ten minutes by a marked increase in the amount of milk secreted. The fat was also increased, being 5.5 per cent. as compared with 3.4 per cent.

Nutritional disturbances on breast-feeding are considered by Myers<sup>14</sup> as not infrequently due to faults in the mother's diet. In this he disagrees with many recent writers, among them Van der Bogert,<sup>15</sup> who believes that any food, whether or not it contains acid, may be allowed unless it causes indigestion in the mother. Myers reports three cases illustrating his theory, where restlessness, diarrhea, or colic in the infant disappeared when fruits and vegetables were omitted from the diet of the mother. The food giving most disturbance he finds to be those containing the largest amount of high flavors; among these he includes fruits, spices and highly flavored vegetables. Fruit both cooked and uncooked has proved injurious. He has noticed a great variation in the sensitiveness to these substances as displayed by different babies, or by the same baby at different ages. He advises that from the beginning of lactation until the end of the first month the use by the mother of the foods named should be limited; and that after this time the addition of vegetables and fruit to the diet should be made very cautiously, only one new article being tried at a time.

Neff<sup>16</sup> advises that in certain disturbances in breast-fed infants, especially in those characterized by abdominal distention, colic, fretfulness, loose stools, and failure to gain, fat-free breast milk should be tried. He believes that it is also indicated in many cases with vomiting, both in those with and without pyloric obstruction, in cases of infantile eczema and of congenitally weak and premature infants. The infants are allowed to nurse a few minutes at the breast, this serving to keep



the milk secretion active. After each nursing all the remaining breast milk is expressed from the breast; this is kept on ice till the cream is separated; the skimmed breast milk is then given as supplementing each nursing.

*Studies in the Distribution of Breast Feeding and Its Relation to Infant Mortality*

Hirsch<sup>18</sup> studied the histories of the feeding of all of the children of the women visiting the ambulatorium of the Frauenklinik at Munich, and found a very low rate of breast feeding: 57 per cent. of the children were not nursed at all; only 33 per cent. were nursed longer than one month; 20 per cent. longer than three months, and 13 per cent. longer than six months. The influence on the infant death rate was shown by the fact that of those who died, only 3 per cent. were breast-fed over six months, while 74 per cent. were not nursed at all.

The statistics from the Lemberg clinic, reported by Lateiner-Mayerhofer and Progulski,<sup>19</sup> show a marked contrast, as here the proportion of babies breast-fed is very high. Only 10 per cent. of the infants were nursed less than six months, while 55 per cent. were nursed one year and many longer. Mixed feeding, which was often injudicious, was frequently given, almost regularly after the sixth month. The mortality among the breast-fed was 16 per cent., among the artificially fed 34 per cent. The authors call attention to the fact that though breast feeding is so general in Galicia (as illustrated by these figures) the infant death rate is very high, being over 20 per cent. This high rate they attribute to the very bad economic and hygienic conditions. They believe that hygienic instruction of the inhabitants could accomplish much.

Rohmer<sup>20</sup> found in Cologne that among married women from 82 to 69 per cent. nursed their babies. Of illegitimate infants, only 31 per cent. were breast-fed after the sixth week.

Among 100 French women who were unable to nurse their infants for some reason, Deresse<sup>10</sup> found that in twenty insufficient milk or disease was the cause, in seventy-three the social position of the mother, in seven egotism or the prejudice of the mother.

Churchill<sup>21</sup> has studied the relation of the feeding of breast milk to the mortality in an infant hospital for a period of three years. He found that the rates of mortality among the infants exclusively breast-fed and those fed exclusively on cow's milk were 36.3 and 36.9, respectively. This practical identity in the rate could be explained by the fact that the infants who had received exclusively breast milk were on an average younger and weighed less than those who had received cow's milk. The death rate of the babies receiving cow's milk who were of equally low weight was considerably higher than that of the infants receiving breast milk.

## ARTIFICIAL FEEDING IN GENERAL

22. Pritchard: *Brit. Jour. Child. Dis.*, 1914, xi, 49.
23. Heubner: *Ztschr. f. Kinderh.*, 1914, xi, 81.
24. Samelson: *Ztschr. f. Kinderh.*, 1914, xi, 86.
25. Mayerhofer and Roth: *Ztschr. f. Kinderh.*, 1914, xi, 117.
26. Gittings: *Arch. Pediat.*, 1914, xxxi, 696.
27. Chapin: *Jour. Am. Med. Assn.*, 1914, lxiii, 1177.
28. Mendel: *Jour. Am. Med. Assn.*, 1914, lxiii, 819.
29. Osborne and Mendel: *Jour. Biol. Chem.*, 1914, xvii, 325.
30. Osborne and Mendel: *Jour. Biol. Chem.*, 1914, xvii, 401.
31. Editorial: *Jour. Am. Med. Assn.*, 1914, lxiii, 247.
32. Niemann: *Jahrb. f. Kinderh.*, 1914, lxxix, 274.
33. Mendel: *Biochem. Bull.*, 1914, iii, 156.
34. Osborne and Mendel: *Jour. Biol. Chem.*, 1914, xvi, 423.
35. Funk: *Ergebn. d. Physiol.*, 1913, xiii, 124.
36. Funk: *Die Vitamine*, Wiesbaden, 1914.
37. Funk: *München. med. Wchnschr.*, 1913, ix, 2614.
38. Schaumann: *Arch. f. Schiffs- u. Tropenhyg.*, 1914, xviii, 125; *Ztschr. f. Kinderh. (ref.)*, 1914, viii, 115.
39. Wheeler and Biester: *AM. JOUR. DIS. CHILD.*, 1914, vii, 169; Wheeler: *AM. JOUR. DIS. CHILD.*, 1915, ix, 300.
40. Peiser: *Berl. klin. Wchnschr.*, 1914, li, 1165.
41. Smith: *Arch. Pediat.*, 1914, xxxi, 784; LeWald: *AM. JOUR. DIS. CHILD.*, 1915, ix, 1261.
42. Kerr: *New York Med. Jour.*, 1915, ci, 296.
43. Variot: *Ztschr. f. Kinderh. (ref.)*, 1914, viii, 281.
44. Müller and Schloss: *Med. Klin.*, 1914, x, 276.
45. Müller and Schloss: *Jahrb. f. Kinderh.*, 1914, lxxx, 42.
46. Leopold: *AM. JOUR. DIS. CHILD.*, 1914, viii, 196.
47. Friedenthal: *Berl. klin. Wchnschr.*, 1914, li, 727.

For the determination of the proper amount of food to be given, the caloric method is again advised by many authors. Several of these draw attention to Howland's work which showed that the caloric needs of infants making active movements and crying is greater than those of infants at rest. Pritchard<sup>22</sup> believes that infants who are overheated by too warm rooms or too thick clothing require less food than infants properly cared for.

Heubner<sup>23</sup> states that to obtain in the artificially fed infant a rate of gain equal to that in the breast-fed a higher number of calories is required. Samelson<sup>24</sup> does not agree with this conclusion.

Mayerhofer and Roth,<sup>25</sup> basing their statements on observations of twenty-three infants so fed that they show very good weight curves, conclude that a perfect uniformity in the caloric needs of infants does not exist. There are many infants who gain best when the calories given fall below the standard of 100 calories per kilogram of body-weight recommended by Heubner; other infants thrive only on an energy quotient far above 100. Heubner's standard, they consider, is the best foundation for the comparison of different forms of food.

The fact that the caloric needs vary with different infants is also emphasized by Gittings;<sup>26</sup> he finds that atrophic children especially

require a higher energy quotient than that corresponding to their weight. He believes that a caloric standard is a useful check in artificial feeding; for if the caloric value is much above or below the average, harm will result in the majority of cases. In Chapin's<sup>27</sup> opinion, the experiments on animals showing the different results obtained with different foods which yield the same number of calories should be a warning not to ascribe too much importance to the caloric method.

The interesting experimental studies made this year as to the influence of different food elements on nutrition and growth, and on the disturbances produced by the absence of certain necessary substances or vitamins in food, have been frequently commented upon in pediatric literature.

Chapin<sup>27</sup> believes that in infant feeding the facts brought out by experimental studies in nutrition should be borne in mind; that a food may be very unscientific (even though exactly prepared with some supposed chemical or caloric requirement in mind), in case some necessary element has been omitted. He warns against the intricate and profound chemical manipulation of food, and believes that the latest scientific studies point favorably to great simplicity in the preparation of artificial food for infants. In feeding he believes that cow's milk should be simply diluted in the right proportion for the age, keeping in mind the fact that none of the ingredients, protein, fat or carbohydrate must be long reduced below what is known to be their average content in human milk.

The important studies of Osborne and Mendel<sup>28, 29</sup> have thrown much light on the problems of the nutrition of the growing infant. Of the amino-acids into which the ingested protein is broken down during digestion and metabolism, almost all are necessary for growth; only certain ones are, however, necessary for maintenance of life. Tryptophan is one of the latter. Zein, contained in maize, does not contain tryptophan, and does not maintain life in animals if fed as the only protein. If tryptophan is added to the food, the animals will live. Lysin has been found by these authors to be essential for growth. Gliadin, which is deficient in lysin, maintains life in adult animals, but will not cause growth in young animals. If lysin is added to this diet the animals grow. Zein, which lacks tryptophan, is also lacking in lysin; Mendel concludes that this fact explains why corn is poorly suited to the growing individual. Proteins like casein, lactalbumin and egg vitellin, which in nature are concerned with growth, are rich in lysin; these, with edestin from hemp seed, are capable of satisfying the nitrogenous needs of all states of development. For growth certain fats have been found by these investigators<sup>28, 30</sup> to be essential. Growing animals fed on isolated food substances with fat in the form of

lard, stopped growing; growth, however, was restored if butter fat was added. Butter fat, egg yolk and cod liver oil contain the ingredient which promotes growth; almond oil and lard do not. The former foods, they remark, have long had the reputation of being efficient foods. They believe that it is improbable that their special potency resides in the triglycerids present. Their work has been commented on<sup>31</sup> as throwing light on the experiments of Niemann<sup>32</sup> in adding butter fat to the diet of infants.

The tendency to grow is, according to Mendel,<sup>33</sup> dependent on hereditary factors; food gives a range of play, but does not influence it permanently. Osborne and Mendel in their experiments on rats, have by various means stopped growth, without causing a permanent loss of ability to grow. They conclude that the tendency to grow apparently does not disappear until the fundamental tendency of the organism is used up.

The term "vitamine" was first used by Funk to describe certain substances present in food in small quantity but necessary to nutrition "which can not be expressed in terms of protein, fat and carbohydrate, or in calories of energy" (Mendel<sup>28</sup>). Mendel believes that classing these unknown substances under the name of vitamins does not explain the disturbances arising from their absence from the diet. Funk<sup>35, 36, 37</sup> has written much on the subject. He describes vitamins as crystalline bodies of very complicated structure containing nitrogen, which can be isolated by different precipitating agents. These bodies are necessary for life; they are thermolabile and are present in very small amounts. They are biologically if not chemically associated. Vitamins are present in the polishings of rice and in milk. Among avitaminoses or deficiency diseases, due to a lack of vitamin in the food, he classes beriberi, scurvy, Barlow's disease, pellagra and rachitis, *Mehlnährschaden* and many other syndromes.

Schaumann<sup>38</sup> considers that Funk's conclusions in regard to all these diseases are theoretical, and have not yet been proven.

Wheeler and Biester<sup>39</sup> have studied experimentally certain proprietary foods used in infant feeding with the object of determining whether they will sustain life and growth when used as exclusive foods; and if not whether the fault lies in a lack of the essential amino-acids, or in the absence of essential accessory substances or vitamins.

Many authors warn against one-sided diets; especially against those very rich in carbohydrate but poor in fats which have been extensively used. Chapin<sup>27</sup> believes that the withdrawal of the fats brings with it especial danger of rachitis.

Niemann<sup>32</sup> believes that fat in the diet is especially necessary for the accumulation of body fat; and that the diets very rich in carbohydrate

tend to decrease immunity. Peiser<sup>10</sup> reminds us that the feeding of normal infants on diets poor in fat and rich in carbohydrate is not "economical"; and that the resulting increased water content of the body tends to lower the immunity.

### *Technic*

Smith<sup>11</sup> believes the posture of the baby during feeding is very important; and advises that immediately before and after feeding the baby should be held upright in order that swallowed air may be expelled. Many infants, he finds, swallow large quantities of air with their feeding. With the baby in the recumbent position fluid gravitates to the posterior portion of the stomach covering the cardiac orifice; the air therefore cannot escape through the esophagus, and leads by pressure to vomiting and colic.

### ARTIFICIAL FEEDING OF THE NORMAL INFANT

The simple milk dilutions, so widely used, are very little discussed in the literature.

Kerr<sup>12</sup> favors top-milk mixtures. Variot<sup>13</sup> gives during the first five or six weeks one part of water to two of milk; in the third month one part of water to three of milk; at the fourth to the fifth month milk is given undiluted. Müller and Schloss<sup>14</sup> give directions for the preparation in the private house of the most important of the milk mixtures.

Two foods were described in this review last year which had been suggested as being superior to the simple milk dilutions in feeding the normal infant: Friedenthal's milk and the whey-modified milk of Schloss. Both have been developed on the principle of imitating breast milk as nearly as possible. Müller and Schloss<sup>15</sup> criticize the article by Bahrdt on Friedenthal milk, on the grounds that according to Bahrdt's analyses the salts in this milk do not resemble, as they are supposed to do, those of breast milk either in total content or in the relative proportions of the various salts; and that the clinical results reported are inconclusive because there were but few young infants fed on the mixture, and because the duration of the feeding was too short. They describe the stages in the development of the "whey-modified milk" of Schloss. They have found that a simple dilution of milk and cream with the addition of potassium chlorid forms a food very similar in composition to that of human milk, both in absolute salt content, and in the relationship of the various ions. They have found that milk-sugar, which they added at first, often leads to bad results, especially in infants' hospitals; they have therefore added dextrin and maltose as the carbohydrate. They discuss the various attempts which have been made during the development of infant feeding to produce an artificial food similar to breast milk.

Leopold<sup>46</sup> has described his results in the use of the whey-modified milk of Schloss. The preparation of the two mixtures prescribed by Schloss are once more described.

Mixture A, for infants under three months, consists of:

Twenty per cent. cream.....	140	c.c.
Whole milk .....	140	c.c.
Water .....	700	c.c.
Potassium chlorid .....	0.2	gm.
Dextrin and maltose.....	35.0	gm.
Flour .....	15.0	gm.
Nutrose or plasmon.....	5.0	gm.

In Mixture B, for infants over three months: the flour is omitted, and the dextrin and maltose is increased to 50 to 70 gm.; otherwise mixtures A and B are the same. During the past year Leopold has given this feeding to fifty-four infants, varying in age from 2 days to 13 months. Sixteen were under 1 month. Two died; one from double otitis media, one from peritonitis. The milk was given in the same amounts as breast milk. The stools were alkaline, yellow, homogeneous and pasty. Leopold has found that infants over 6 months do not gain well on this feeding. He considers that the food is especially indicated for very young infants for whom breast milk is not obtainable. Of the fifty-four cases, in thirty-six the result was good; in ten fairly good, in eight poor. He concludes that the results with this feeding are much better than with any other method of artificial feeding.

Friedenthal<sup>47</sup> writes that in foods for infants the correlation of salts is more important than the total ash content of the milk. The low salt content of human milk is the optimum for the normal child.

#### ARTIFICIAL FEEDING OF THE SICK INFANT

48. Lichtenstein: *Hygiea*, 1914, lxxvi, 17; *Monatschr. f. Kinderh.* (ref.), 1914, xiv, 7.
49. Modigliani: *Pediat.*, 1914, xxii, 405.
50. Di Cristina: *Pediat.*, 1914, xxii, 161.
51. Langstein: *Jahreskurs. f. ärztl. Fortbild.*, 1914, v, 54.
52. Sluka and Sperk: *Wien. klin. Wchnschr.*, 1914, xxvii, 833.
53. Aschenheim: *Therap. Monatsh.*, 1914, xxviii, 435.
54. Kern and Müller: *Berl. klin. Wchnschr.*, 1913, l, 2237.
55. Soldin: *Berl. klin. Wchnschr.*, 1914, li, 794.
56. Leichtentritt: *Arch. f. Kinderh.*, 1914, lxiii, 61.
57. Rost: *Arch. Pediat.*, 1914, xxxi, 849.
58. Beck: *Med. Klin.* 1914, x, 149; *Ztschr. f. Kinderh.* (ref.), 1914, viii, 129.
59. Lust: *Ztschr. f. Kinderh.* (ref.), 1914, viii, 129.
60. Moro: *Ztschr. f. Kinderh.* (ref.), 1914, viii, 129.
61. Ostrowski: *Jahrb. f. Kinderh.* (ref.), 1914, lxxix, 374.
62. Wegener: *München. med. Wchnschr.*, 1914, lxi, 359.
63. Kamnitzer: *Deutsch. med. Wchnschr.*, 1914, xl, 855.
64. Bosworth and Bowditch: *AM. JOUR. DIS. CHILD.*, 1914, viii, 120.
65. Miller: *Arch. Pediat.*, 1914, xxxi, 772.
66. Eaton: *Arch. Pediat.*, 1914, xxxi, 452.
67. Dunn: *AMER. JOUR. DIS. CHILD.*, 1915, ix, 225.
68. Dunn: *Boston Med. and Surg. Jour.*, 1915, clxxii, 167.

*Albumin Milk*

The value of this food and its substitutes in the feeding of sick infants is once more attested by many authors. Lichtenstein<sup>48</sup> reports fifty cases, for the most part cases of severe nutritional disturbance, treated with albumin milk. The results were in the main very good. He found it possible usually to change to another diet after two to three weeks.

Modigliani<sup>49</sup> reports good results with albumin milk in the feeding of six infants with dyspepsia, intoxication and balance disturbance, as shown by a gain in weight, cessation of fermented stools, and the appearance of fat-soap stools. Two breast-fed infants with dyspepsia recovered when albumin milk was fed as a supplementary food. The results when albumin milk was used in the feeding of eight new-born infants were very bad.

Di Cristina<sup>50</sup> has had more favorable results in feeding albumin milk to normal infants. He used it also in all cases of nutritional disturbance. In chronic dyspepsia he has seen a prompt improvement in all the symptoms; in these cases where the weight remained stationary fat and sugar were added.

Langstein<sup>51</sup> writes that for severe cases of nutritional disturbance albumin milk is superior to casein calcium milk. Sluka and Sperk<sup>52</sup> found that feeding with albumin milk was more successful with dispensary cases than with hospital infants. The poor results with the latter they ascribe to "hospitalism."

*Substitutes for Albumin Milk*

In all the preparations the object has been to obtain a mixture with a low salt and sugar content, and a high percentage of protein and calcium.

With regard to the many substitutes for albumin-milk, Finkelstein (see Footnote 137) writes that he prefers those which contain casein in fine, freshly precipitated flakes. The powdered casein preparations, such as casein calcium, plasmon, etc., may become hard and tough.

Aschenheim<sup>53</sup> has suggested a new modification of albumin milk.

Kern and Müller<sup>54</sup> have also proposed a new substitute. One liter each of buttermilk and water are boiled together and the amount filled up to two liters. The mixture on standing shows a precipitation of the casein, and a formation of clear whey; 1125 gm. of the whey are removed, and 125 gm. of 20 per cent. cream are added to the remainder, together with sugar from 5 to 7 per cent. The advantages claimed for this food are its freshly precipitated casein and its content of lactic acid.

Soldin<sup>55</sup> has prepared a similar protein-rich food. Half a liter of milk is allowed to sour; the cream is removed, and the milk is warmed

to 40 C. The casein which is precipitated is separated by a sieve, and is then added to 0.5 liter of sour milk and 0.5 liter of water or flour water with sugar. The food is prepared easily and is cheaper than albumin milk. The clinical results have been good.

Leichentritt<sup>56</sup> describes the preparation of Engel's modification of albumin milk, which was reviewed last year. His results with this feeding were good, as he shows by case histories.

Casein-calcium milk has been used to a considerable extent.

Rost<sup>57</sup> reports fifty-six dispensary cases of summer diarrhea treated with a mixture prepared according to Stoeltzner's directions. Of the casein-calcium preparation 20 gm. are added to  $\frac{1}{3}$  of a pint of milk;  $\frac{2}{3}$  of a pint of milk is heated; the cold solution is added and the whole brought to the boiling point; one pint of boiled water or cereal decoction is added. Rost rarely added sugar (in the form of dextrin-maltose) before the third day. The histories of the cases show that the results were, in the main, good. Twenty-seven showed gain in weight. Rost recommends this food on account of the simplicity of the preparation and its cheapness as particularly useful in the treatment of dispensary cases.

In acute and sub-acute dyspepsia Beck<sup>58</sup> has had as good results with casein calcium milk as with albumin milk; in intoxication, however, the results have been less good. Lust,<sup>59</sup> in discussing Beck's report, states that his own results with casein-calcium milk has been very unequal. He does not believe that this preparation replaces albumin milk. Moro,<sup>60</sup> too, found that in older infants and less severe cases the results were excellent; he has seen some bad effects of casein-calcium milk in other cases.

Ostrowski<sup>71</sup> fed with casein-calcium milk forty-nine infants with the different nutritional disturbances; his results were very good. Wegener<sup>62</sup> used this food successfully in twenty-two cases. Kamnitzer<sup>63</sup> reports eighteen cases in which casein-calcium milk was used; two very young infants with intoxication died. In the others, however, there was improvement, the stools becoming formed on the second to fifth day. Langstein<sup>51</sup> has noted, in slight and moderate cases of nutritional disturbances, results with casein-calcium milk equal to those of albumin milk; in severe cases, as already noted, albumin milk is superior.

In connection with these methods for increasing the proteid content of a milk mixture, the preparation of dry powdered paracasein, as described by Bosworth and Bowditch,<sup>64</sup> is interesting. Very large quantities of this substance, when fed to an infant, led to no toxic symptoms nor fever.



*Other Diets*

The diets of the group including albumin milk and its substitutes are in general recommended chiefly for those disturbances ascribed to the harmful action of too high concentrations of sugar and salt. For disturbances associated with an intolerance for fat, other diets are recommended.

For these cases Miller<sup>65</sup> and Eaton<sup>66</sup> write of the good effects of a diet rich in protein and carbohydrate, and poor in fat. Miller<sup>65</sup> gives at first a diet with a very low percentage of fat (0.5 per cent.) moderate protein (from 1.3 to 1.5 per cent.) and high carbohydrate (from 5 to 6 per cent.). The fat is increased very slowly, the proteid and carbohydrate more rapidly. On this diet infants show putty-like stools and make a marked improvement. Eaton<sup>66</sup> also reports infants doing well on a diet with very little fat. For cases of fat intolerance, both acute and chronic, Dunn<sup>67, 68</sup> advises a diet rich in protein (3 per cent.) with moderate carbohydrate (7 per cent.) (which should be in the form of maltose) and very low fat. For some cases he considers breast milk essential. Niemann,<sup>62</sup> basing his method on his theory that injury by fat is due to its content of the lower fatty acids, recommends feeding infants with fat intolerance on mixtures made up from skimmed milk and washed butter. By washing butter thoroughly, and kneading it as the wash water is renewed eight or ten times, it may be largely freed from the lower fatty acids. He has used the following diet:

500 gm. skimmed milk.  
500 gm. 5 per cent. flour water (mondamin).  
50 gm. malt extract.  
50 gm. washed butter.

Peiser<sup>40</sup> has made experiments to determine which fats are best tolerated by infants. Using buttermilk with flour as the medium, he has added (usually for eight-day periods) different kinds of fats: cod liver oil, salt-free butter, 15 per cent. cream and many other oils. The impression gained from his results is that cod liver oil is tolerated the best, butter and cream the least well.

## THE ETIOLOGY OF NUTRITIONAL DISTURBANCES OF INFANTS

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70. Rietschel, Heidenhain and Ewers: *München. med. Wchnschr.*, 1914, lxi, 648.
71. Lövegren: *Ztschr. f. Kinderh.*, 1914, xii, 110.
72. Moro: *Jahrb. f. Kinderh.*, 1914, lxxix, 645.
73. Hahn and Moro: *Jahrb. f. Kinderh.*, 1914, lxxix, 664.
74. Hayashi: *Jahrb. f. Kinderh.*, 1914, lxxix, 674.
75. Klocman and Moro: *Jahrb. f. Kinderh.*, 1914, lxxix, 676.
76. Luna: *Pediatrics*: 1914, xxii, 88.
77. Gismondi: *Pediatrics*, 1914, No. 4; *rev. Arch. Pediat.*, 1915, xxxii, 151.
78. Sherman and Johnes: *Arch. Pediat.*, 1914, xxxi, 749.

79. Southworth: Jour. Am. Med. Assn., 1914, lxiii, 1375.
80. Freudenberg: Monatschr. f. Kinderh., 1914, xiii, 141.
81. Schlutz: Journal-Lancet: 1914, xxxiv, 178.
82. Brüning: Jahrb. f. Kinderh., 1914, lxxix, 305.
83. Thomas: Biochem. Ztschr., 1913, lvii, 456, 473.
84. Bahrdt and McLean: Ztschr. f. Kinderh., 1914, xi, 143.
85. Huldshinsky: Ztschr. f. Kinderh., 1913, v, 475.
86. Benjamin: Jahrb. f. Kinderh., 1914, lxxx, 545.
87. Lesné: Ztschr. f. Kinderh. (ref.), 1914, viii, 117.
88. Lust: München. med. Wehnschr., 1913, lx, 2720.
89. Lust: Jahrb. f. Kinderh., 1913, lxxvii, 383.
90. Lawalschek: Prag. med. Wehnschr., 1914, xxxix, 185.
91. Hayashi: Monatschr. f. Kinderh., 1914, xii, 749.
92. Modigliani and Benini: Policlinico, 1914, xxi, No. 51; (rev.) Jour. Am. Med. Assn., 1915, lxiv, 475.
93. Poulsen: Jahrb. f. Kinderh., 1914, lxxix, 77.
94. Uffenheimer: Jahrb. f. Kinderh., 1914, lxxx, 543.
95. Uffenheimer: Jahrb. f. Kinderh., 1914, lxxix, 92.
96. Liwshiz: Dissertation, Munich, 1913.

The two main causes of the nutritional disturbances in infancy, food and bacterial infection, have been discussed as in previous years.

The influence of the various foodstuffs in the etiology of the nutritional disturbances of infants is always a fruitful subject of discussion in pediatric literature.

#### *Influence of Food and Foodstuffs: Salts*

The whey salts in cow's milk are considered by most German writers as being extremely important in causing nutritional disturbances.

The much-mooted question of salt fever is still debated. Heubner,<sup>70</sup> although acknowledging the importance of the freshness and sterility of the diluting fluid in preventing a rise of temperature after the subcutaneous injection of salt solution, still believes that the results of certain experiments speak for the action of an excess of sodium chlorid in causing fever.

Rietschel, Heidenhain and Ewers<sup>71</sup> deny that all cases of fever arising after the subcutaneous injection of salt solution may be ascribed to bacteriotoxic substances in the distilled water used, and believe that in some cases an inorganic constituent such as copper may be the cause. In proof of this theory they report that 58 per cent. of the infants injected with freshly distilled solutions which had been boiled with bits of copper showed a rise in temperature.

Finkelstein has believed that the alimentary fever occurring in young infants and in those with nutritional disturbances after the taking by mouth of salt solution is caused by a biochemical action of the salt on the organism, and not, as thought by some authors, that this fever is due to bacterial factors, becoming active after an injury to the intestinal epithelium by the salt. Lövegren<sup>72</sup> believes that this question

can not be settled clinically; he has therefore subjected it to experiment. In healthy dogs, during the height of digestion, he has injected salt and sugar solutions directly into the mesenteric veins, thus excluding any action of the salt on the intestinal epithelium. In these operations the greatest care was used to maintain asepsis; the solutions used were made from freshly distilled water and then autoclaved; for most of the distillations a glass apparatus was used. Experiments were made with hypertonic, hypotonic and isotonic salt solutions, with distilled water, with lactose and dextrose solutions, and with other solutions. In eleven cases in which a hypertonic solution was injected there was ten times a rise of temperature; one case with hypotonic solution also showed a rise; while in one case each injected with an isotonic solution and with Ringer solution the reaction was weak. He concludes that in his experiments the fever must be due to a direct action of an anisotonic solution on the body cells.

It does not seem excluded that the rise in temperature (averaging 1.1 C.) may not have been due to the operative procedure; the two cases used as controls, in which an isotonic solution and Ringer's solution were injected, which showed but a slight rise in temperature, seem insufficient.

Moro<sup>72</sup> and his co-workers<sup>73, 74, 75</sup> have made an interesting series of experimental studies in regard to the action of whey salts on the intestinal epithelium.

### *Carbohydrate*

Luna<sup>76</sup> writes that infants with a flatulent dyspepsia, and positive fermentation test as applied to the stools reveal an intolerance of carbohydrate. These children should be fed very little carbohydrate and much albumin.

In regard to which form of sugar is least likely to cause nutritional disturbance, Gismondi<sup>77</sup> believes that a healthy child is able to digest lactose, saccharose and maltose equally well. He proposes giving a mixture of the three varieties, the object being not to exceed the limit of tolerance of each kind. Sherman and Jones<sup>78</sup> have tested the various sugars for their effect on the gastric secretions of fifteen infants. They conclude from their results that malt sugar in the form of dextrin maltose is at least twice as stimulating to gastric secretion as milk sugar or cane sugar.

That starch has a protective action against the injurious effects of both sugar and fat is claimed by Southworth.<sup>79</sup> He does not agree with the view that the beneficial results obtained by the use of starch gruels is due solely to their prevention of the formation of tough curds. He believes that there are several ways in which starch may influence digestion. The protective action of starch is shown by the benefit

derived from its use in malt-soup, which contains a high proportion of sugar. He believes that the slow breaking down of starch gives less opportunity for fermentation.

The symptom complex of *Mehlnährschaden*, due apparently to a diet consisting too exclusively of carbohydrates, has been much discussed. Funk, as previously stated, has included this disturbance among the "avitaminoses" or deficiency diseases. This view has been opposed by Schaumann, and especially by Freudenberg.<sup>80</sup> The latter finds fault with Funk's hypothesis, which attributes to a lack of vitamins a disease so plainly associated with a lack of many of the constituents of a sufficient food. Schlutz<sup>81</sup> reports a case illustrating the hypertonic form of this disease. A child 14 months old, fed for two months on a gruel without milk, developed edema, stiffness and contractures, but recovered on breast milk. Brüning<sup>82</sup> has contributed to our experimental knowledge of this disturbance. White rats, fed on a one-sided carbohydrate diet, showed on an analysis of the body tissues a greater amount of water and a higher relative amount of salt. He shows that these findings correspond with the clinical condition in *Mehlnährschaden*.

Niemann<sup>82</sup> and Peiser<sup>40</sup> comment on the reduction in immunity caused by a one-sided carbohydrate diet. This loss of immunity has frequently been commented on. Thomas<sup>83</sup> found that young pigs fed chiefly on carbohydrate showed a marked lessening of resistance to tuberculosis, while those fed chiefly on protein showed a limitation of the tuberculous process. Langstein<sup>115</sup> remarks on this work as being an experimental confirmation of the clinical facts recorded by him of the especially favorable course of infections, especially of tuberculosis in infants, when protein forms a large part of the diet. He warns, however, against drawing conclusions from experiments.

### *Fat*

Two nutritional disturbances are ascribed to a high percentage of fat in infant-feeding: an acute, and a chronic disturbance.

Dunn<sup>67, 68</sup> describes cases showing an intolerance for fat, which he believes are caused more often originally by an overfeeding with carbohydrate than by one with fat. These cases are frequently ones of extreme malnutrition. They show their lack of tolerance for fat by the facts (1) that they do not gain in weight on diets low in fat, yet when it is added give evidence of failure to absorb it by the presence of free fat or excessive soap in the stools, and (2) that a further increase in fat in the diet leads to acute disturbances with vomiting, diarrhea, and frequently with collapse. The treatment recommended by Dunn for these cases has already been spoken of.

Niemann<sup>82</sup> describes the two classes of disturbance caused by fat:

acute disturbances associated with diarrhea and chronic disturbances or *Milchnährschaden*. There is some ground for believing that the reason why cow's milk fat is so much more apt than the fat of breast-milk to cause disturbances of both types is the fact that cow's milk contains more of the lower volatile fatty acids. In proof of this theory he shows that children who cannot take milk-fat with safety may be fed large amounts of oil, and that the best oils are those low in the lower, volatile fatty acids.

The relation of the volatile fatty acids to the nutritional disturbances is a very complicated one. Bahrdt and McLean<sup>84</sup> have studied this subject. They have shown that diet influences greatly the content of the stools of normal infants in free volatile fatty acids. In those of breast-fed infants the percentage was high; in those of artificially fed infants free volatile fatty acids are absent. In the stomach contents of normal infants on the two types of feeding the proportions are, however, reversed; in the stomach contents of infants on cow's milk there is from three to six times as much volatile fatty acid as in those of infants on breast milk. This result may probably be explained by the fact that the origin of the volatile fatty acids is quite different in stomach and in intestine. In the stomach they arise normally almost exclusively by a fermentative splitting of pre-formed butyric or caproic; of this breast milk has less than cow's milk; in the intestine the acids are formed mainly by bacterial action on the sugars and also on the higher fatty acids. The authors found no free volatile fatty acids in the stools even when sugar or cream were added to the diet of artificially fed infants. These acids were found, however, to be present free in every case in the stools of artificially fed infants with acute nutritional disturbances and in such concentration that the authors believe that these acids have some pathologic action in stimulating peristalsis.

Huldschinsky<sup>85</sup> studied the content of volatile fatty acids in the stomach contents of infants with gastro-enteritis, or suffering from overfeeding. He reports that rarely was there an increase as compared with the stomach contents of normal children. He believes that these acids can only be looked on as injurious in cases in which the stomach is already disturbed in function.

### *Protein*

There has been little written this year in regard to a directly harmful action of protein in the diet of infants.

Benjamin<sup>86</sup> found that large doses of "plasmon," a preparation of protein, caused protein fever in infants. Lesné<sup>87</sup> writes of acute cases of alimentary hypersensitiveness, both slight and severe, usually induced by eggs and cow's milk. The severe cases showed a

rapid pulse, fall in temperature and collapse. Lust<sup>88</sup> warns against the common practice of feeding egg albumin water in the treatment of acute nutritional disturbances in infants. In the course of his experiments in regard to the permeability of the intestinal tracts of infants to unchanged protein, he fed twenty normal infants the white of one-half to one egg; in a few cases that of two eggs. Sixteen of the children showed some gastro-intestinal symptoms; some showed frequent thin stools. Three infants showed edema and urticaria.

Lust's<sup>89</sup> work was reviewed last year. To discover whether or not protein passes through the intestinal epithelium unchanged he used the following test: The urine and in some case the blood serum of the infants fed on certain proteins were tested with a serum having a strong precipitation titer for the protein which had been fed. He found that in cases of acute and chronic nutritional disturbances in infants, egg albumin frequently passed through the intestinal wall unchanged.

Lawatschek<sup>90</sup> has had similar results, using the same tests. Among twenty-nine older infants tested, in cases of slight nutritional disturbance, he found no passage of unchanged protein; in severe disturbances, he obtained markedly positive reactions. He believes that there is a parallelism between the degree of the reaction and the outcome of the disease, and believes that the test may be used to determine the prognosis. Lawatschek, like Ganghofner and Langer previously, found that new-born infants up to the tenth day constantly gave evidence of the passage of unchanged foreign protein through the intestinal wall. All of the new-born infants who did not vomit the egg albumin gave positive reactions.

Hayashi<sup>91</sup> has attempted to determine the limit of tolerance of the intestine of twenty-eight normal infants for egg albumin, using the same technic as Lust. He has found that when from 15 to 20 gm. egg albumin are given to the normal infant, the unchanged proteid can usually be demonstrated in the urine. This limit of tolerance he has not found to undergo much change during the first year. In infants with exudative diathesis and in infants who have recovered recently from acute nutritional disturbances he finds a lessening of tolerance. Modigliani and Benini<sup>92</sup> have made similar tests to determine whether the casein of cow's milk ever passes the intestinal wall unchanged. They obtained positive results in the case of infants, both new-born and older infants with gastro-intestinal disturbances who were fed on cow's milk.

The question of the presence of casein and paracasein in the stools of infants has been studied still further by Poulsen,<sup>93</sup> Uffenheimer<sup>95</sup> and Liwschitz.<sup>96</sup>

## INFLUENCE OF BACTERIA ON NUTRITIONAL DISTURBANCES

97. Day and Gerstley: *Am. Jour. Dis. Child.*, 1915, ix, 233.
98. Young: *Arch. Pediat.*, 1914, xxxi, 753.
99. Breuning: *Jahrb. f. Kinderh.*, 1914, lxxx, 98.
100. Metchnikoff: *Ann. de l'Inst. Pasteur*, 1914, xxviii, 89.
101. Bertrand: *Ann. de l'Inst. Pasteur*, 1914, xxviii, 121.
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103. Bluhdorn: *Monatschr. f. Kinderh.*, 1914, xiii, 37.
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105. Schelble: *Jahrb. f. Kinderh.*, 1914, lxxix, 507.
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107. Bobillier: *Thèse de Paris*, 1913, No. 327; *Ztschr. f. Kinderh. (ref.)*, 1914, viii, 191.
108. De Buys: *Jour. Am. Med. Assn.*, 1914, lxiii, 1806.
109. Archibald: *Jour. Trop. Med.*, 1914, xvii, 161.
110. Morse and Talbot: *Boston Med. and Surg. Journal*, 1915, clxxii, 171.
111. Peyri-Rocamora: *rev.*, *Arch. Pediat.*, 1915, xxxii, 159.
112. Logan: *Jour. Path. and Bacteriol.*, 1914, xviii, 527.
113. Editorial: *Jour. Am. Med. Assn.*, 1914, lxiii, 952.
114. Basten: *Ztschr. f. Hyg. u. Infectious-krankh.*, 1914, lxxvii, 282.

That bacteria may cause gastro-enteritis in infants seems now to be a well-established fact; especially is this true of the type of case showing symptoms resembling dysentery. Still unsettled, however, is the question of the relative importance of bacteria in all cases of diarrhea. Morse and Talbot<sup>110</sup> believe that when large numbers of bacteria of the dysentery group or streptococci are found in the stools of cases showing marked disturbance of the intestinal tract, they are in most instances the cause. The presence of a few of these organisms in the stools in diarrhea does not, however, prove that they are the cause, because they may be present in small numbers in the stools of normal infants.

Day and Gerstley<sup>97</sup> have attempted to reconcile the conflicting theories of the cause of infantile diarrhea by showing that different types of cases have different causes. Twenty-two cases of severe diarrhea observed by them are classified into: food disturbances, of which there were two; cases of infectious diarrhea, of which, also, there were but two; and parenteral infections, eighteen cases. The cases of infectious diarrhea were caused by the gas bacillus.

Young<sup>98</sup> reviews the research work of the Boston Floating Hospital during the last few years on the subject of infectious diarrhea in infants. Though clinically the cases show the same picture, they may be divided according to the cause into cases caused by the dysentery bacillus, and those caused by the gas bacillus. The treatment varies according to the cause. In cases caused by the dysentery bacillus, after sterile water for twenty-four hours a 5 per cent. lactose solution is given until the temperature is normal and blood has disappeared from the stools. In extreme cases 2.5 per cent. dextrose

solution is given subcutaneously. Cases caused by the gas bacillus, on the other hand, require a food containing little sugar and a high protein content. The observations of different years show a seasonal variation both in the type of organism and in the degrees of virulence of the same organism.

Breuning<sup>99</sup> examined 117 cases of diarrheal disease in infancy and early childhood for the presence of "paratyphus B." as the cause. In eleven cases the serum was found to agglutinate this bacillus. Three patients were under 1 year. One baby of 6 months developed a metastatic abscess in the shoulder which showed a pure culture of "paratyphus B." bacilli. Breuning advises that more frequent bacteriological examinations should be made in case of acute gastro-enteritis in infants.

Several French observers believe that the *Bacillus proteus vulgaris*, especially in conjunction with other bacteria, may frequently cause infantile diarrhea. Metchnikoff<sup>100</sup> has come to this conclusion, after a series of bacteriologic examinations of stools of infants showing intestinal disturbances. This etiologic significance is present especially when the *B. proteus vulgaris* is associated with another of the intestinal bacteria. The *B. proteus* was also found in normal infants who acted, according to Metchnikoff, as carriers.

Among fifty-five cases of diarrhea examined by Bertrand<sup>101</sup> in the summer of 1912, the *B. proteus vulgaris* was found in all; among twenty-four normal children only twice.

Bertelot<sup>102</sup> agrees with the theory of Metchnikoff.

Several authors have described cases of bacillary dysentery. Blühdorn<sup>103</sup> during 1912 and 1913 saw twenty-four cases in infants and young children. The clinical symptoms were frequently the same as those of disturbances caused by food; severe cases especially, showed a marked resemblance to cases of alimentary intoxication. The cases of dysentery were, however, markedly contagious; sugar was absent from the urine, and breast-fed children were frequently attacked. In different epidemics the following types of cases were observed: simple intestinal catarrh; cases associated with a grip infection; cases without fever, but showing mucus and sometimes blood in the stools; and very severe cases, occurring usually in atrophic children with symptoms either of decomposition or of intoxication. In the treatment, after emptying the gastro-intestinal tract, sterile water is given for a short period, which should not be continued too long in cases debilitated by a long continued cereal water diet. Whey has been used for several years, with good results. Blühdorn advises an examination for the bacilli in all cases suspicious of dysentery. In intoxication the disease should be suspected if the condition does not yield when all food is withdrawn.



Schild<sup>104</sup> made the bacteriologic and serologic examinations, determining the diagnosis in the cases reported by Blühdorn. The bacilli found belonged culturally to the group of pseudo-dysentery bacilli. Some of these strains were agglutinated by well-known races; those isolated from cases in one epidemic, however, could not be identified with any known race of pseudo-dysentery bacilli either by complement fixation or agglutination. Complement fixation was found to be a very sensitive test for the identification of different strains of bacteria.

Schellble<sup>105</sup> reports sixteen cases of acute nutritional disturbances occurring simultaneously in the form of an epidemic among the twenty infants in an institution. Parenteral infection in these cases could be ruled out as a causative factor; the author agrees, however, with Meyer that this is the most frequent factor in nutritional disturbances of infants in institutions. All sixteen infants affected were taking the same milk; the four infants spared did not receive this milk. The stools of the infants affected showed no typhus, paratyphus or dysentery bacilli, and agglutination tests were negative. The author was undecided as to the cause of this epidemic.

The influence of flies in causing infantile diarrhea through the carrying of infection has been the subject of much popular propaganda; the experimental studies in proof of this theory are, however, very few. That carried out by the Bureau of Public Health and Hygiene of the New York Association for the Improvement of the Poor and reported by Armstrong<sup>106</sup> is therefore especially interesting. In the Italian district of the Bronx two areas were selected; in each there were 311 families with 1,725 individuals in one area and 1,744 in the other. The general conditions in the two areas were similar, and there were about the same number of breast-fed infants in each. In one area all known measures for protection against flies were taken; doors and windows were screened, manure was treated with iron sulphate, fly traps were placed, oral and written instructions were given, supplemented by moving picture films. Records of morbidity in the two areas for the period between July 21 and September 13 are interesting. The cases of diarrhea in children under 5 years were twenty in the area protected against flies as compared with fifty-seven in the unprotected area; the total number of days of sickness among these children from this cause were 273 in the protected area and 984 in the unprotected. Armstrong emphasizes the necessity of continuing the investigation on a larger scale and for a longer time.

Amebic dysentery, according to Bobillier<sup>107</sup> is very rare even in the tropics in infants under 2 years, but has been observed in France. Emetin works well in small doses. DeBuys<sup>108</sup> reports eight cases in

young children; the two youngest were 4 years old. The treatment was emetin.

Archibald<sup>109</sup> saw two patients aged 2½ years and 8 months in the same family. For a 2-year-old child he advises emetin 0.01 gm.

### *Bacteriology of the Normal Stools*

Morse and Talbot<sup>110</sup> have summarized the literature in regard to the bacteriology of the gastro-intestinal tract in infancy. Peyri-Rocamora,<sup>111</sup> Logan,<sup>112, 113</sup> and Basten<sup>114</sup> have studied this subject.

#### INFLUENCE OF PARENTERAL INFECTIONS ON NUTRITIONAL DISTURBANCES

- 115. Langstein: Jahresb. f. ärztl. Fortbild., 1914, v, 57.
- 116. Stolte: Jahrb. f. Kinderh., 1914, lxxx, 213.
- 117. Triboulet: Med. Infant., 1914, xxii, 73.
- 118. Grünfelder: Ztschr. f. exper. Path. u. Therap., 1914, xvi, 141.
- 119. Langstein: Ztschr. f. Kinderh. (ref.), 1914, viii, 54.
- 120. Czerny: Ztschr. f. Kinderh. (ref.), 1914, viii, 144.
- 121. Kowitz: München. med. Wchnschr., 1914, lxi, 1321.

The work of Meyer on "hospitalism" was reviewed last year. Langstein<sup>115</sup> refers to this work as proving that the bad influence of hospitals on infants does not depend solely on infections of the intestinal tract or on insufficient care; but depends especially on infections of the respiratory passages ("grip"). These infections predispose greatly to nutritional disturbances, and are so prevalent in infants' institutions that hardly a child remaining for some time in the institution is spared. He writes that nutritional disturbances when occurring together with "grip" should be treated not by taking away the food, but by feeding with albumin milk.

These views of Langstein and Meyer with regard to the cause of "hospitalism" in infants are questioned by Stolte.<sup>116</sup> He believes that more important than infections, in causing the poor results with infants in hospitals, is the lack of personal and individual care. An experiment was made in the children's clinic at Berlin to imitate the care usual in a private home; each infant was put into the special care of one nurse, who was instructed to give wide play to the infants' likes and dislikes as to food. The results were excellent; there was gain in weight, as well as improvement in general condition, color and activity. He concludes that it is possible in a hospital by using this method to achieve as good results as those obtained in private homes.

Triboulet<sup>117</sup> writes of the predisposition to nutritional disturbance associated with certain infections. In uncomplicated pneumonia he believes that the intestine is not necessarily affected; but in severe

pneumonia he has found a regular connection with diarrhea, as also in cases of pneumonia complicated by purulent pleuritis, otitis and peritonitis.

Grünfelder<sup>118</sup> has studied experimentally in dogs the effect of acute infections on the secretion of gastric juice. The formation of Pawlow's "blind stomach" was accomplished in two dogs; fever and infections were induced by causing localized abscesses or by insufflating infectious material into the nostrils. The amount of gastric juice secreted during the infections was found to be greatly reduced; it was more slowly secreted, and showed a diminution in hydrochloric acid. Grünfelder believes that these findings are parallel to the nutritional disturbances occurring in infants in the course of acute infections.

Pyelocystitis is referred to by Langstein<sup>119</sup> as being very frequently associated with anorexia, which may be so marked that feeding by gavage must be resorted to.

The fact that nutritional disturbances likewise predispose to certain infections is referred to by Czerny,<sup>120</sup> especially with regard to paravertebral pneumonia. Kowitz<sup>120</sup> believes that acute alimentary disturbances predispose greatly to pyelocystitis in infants.

#### RELATION OF HEAT AND OTHER FACTORS TO INFANT MORBIDITY AND MORTALITY FROM NUTRITIONAL DISTURBANCES IN SUMMER

122. Schreiber and Dorlencourt: *Arch. de méd. d'enf.*, 1914, xvii, 1.

123. Breyer: *Ztschr. f. Kinderh. (ref.)*, 1914, viii, 158.

124. Prinzing: *Wien. klin. Rundschau*, 1913, xxvii, 678.

125. Japha: *Ztschr. f. Kinderh.*, 1913, vii, 518.

126. Heiman: *Arch. Pediat.*, 1914, xxxi, 466; *AM. JOUR. DIS. CHILD.*, 1914, viii, 138.

128. Helmholtz: *Jour. Am. Med. Assn.*, 1914, lxiii, 1371.

129. Nicolaysen: *Monatschr. f. Kinderh. (ref.)*, 1914, xiv, 10.

130. Rohmer: *Ztschr. f. Sauglingsfürs.*, 1914, vii, 329, 385.

131. Epstein: *Beth. z. med. Klin.*, 1913, No. 9.

For the last few years many studies have been made, especially by German authors, on the subject of the direct action of hot weather in causing nutritional disturbances in summer in infants.

Schreiber and Dorlencourt<sup>122</sup> have observed in young dogs exposed to very high temperatures the same symptoms as in infants with heat prostration.

Many German authors have shown in the last year that housing conditions which favor a high indoor temperature predispose to infantile diarrhea. Breyer<sup>123</sup> and Prinzing<sup>124</sup> again bring forward evidence in proof of this theory. Japha,<sup>125</sup> from results in work at infant consultations, concludes that pure milk cannot protect infants in summer from the dangerous effects of high temperatures, and that

housing improvements and instruction in general hygiene are necessary for this purpose. Heiman<sup>126, 127</sup> has made the experiment of cooling artificially in summer a ward used for infants with nutritional disturbances. The temperature of the room was during the forty-two days of the experiment from 5 to 11 degrees below the outside temperature. Thirteen patients were treated; none of these were premature or moribund infants, as in such cases the treatment seems not to be indicated. One infant died, twelve recovered. Control observations could not be made. Heiman gained the impression that the infants so treated were more comfortable than infants in the other wards.

Helmholtz<sup>128</sup> has made an interesting study of the relation of high indoor temperatures to high body temperature of infants, and to the mortality and morbidity of infants in summer. Maximum and minimum temperatures were recorded in the homes of the forty-six infants studied; a daily call by a nurse was made, the condition of the infant was noted and its temperature taken. In the thirty-nine attacks of dyspepsia observed in twenty-nine infants, there seemed no definite relation between high room temperature and gastro-intestinal disturbance. The average room temperature of the day before and of the day of the onset of the dyspepsia was 89 F. Very high maximum indoor temperatures were observed; in ten cases temperatures over 105 were recorded. The indoor temperatures exceeded the outdoor frequently by marked amounts; once by 40 degrees and five times by 30 degrees. There was, however, no constant relationship between fever in the infant and a high room temperature; as in 80 per cent. of the cases the infants showed in spite of a high temperature in the house a normal range of body temperature. Among the six cases which terminated fatally, only one or two could be ascribed to the direct effect of heat. Helmholtz calls attention to the fact that the clothing of infants varies greatly, and that clothing may act very intensely in producing fatal heat retention, this having been shown recently for experimental animals in the Sprague Institute Laboratory by Drs. McClure and Sauer. He concludes that the study would indicate that an improper adjustment of the individual to the surrounding temperature, rather than the height of the temperature, increases the mortality from gastro-intestinal diseases in summer; and that the aim should be to educate mothers to keep their infants cool in summer.

Nicolaysen<sup>129</sup> has analyzed the statistics of the deaths of infants from diarrhea in Christiania. He found that several such deaths frequently occurred in the same house in the same year. Of six houses in which especially many cases occurred, only one showed

conditions which might lead to overheating; the remaining five showed good ventilation. He concludes that these findings speak for an infectious cause of infant diarrhea, and believes that flies are very important in spreading the disease.

The work of Armstrong<sup>130</sup> with regard to the relation between flies and infantile diarrhea has been mentioned.

Rohmer<sup>139</sup> has made an interesting investigation of the relative importance of different forms of feeding and of housing conditions in causing infant diarrhea in summer. In a number of streets of the older section of Cologne, where the infant mortality was very high, he visited regularly all the infants born, and noted the conditions. Breast-feeding he found to be fairly prevalent; 40 per cent. were breast-fed for nine months. Of children breast-fed in the second half year, 80 per cent. were healthy; of infants not breast-fed or insufficiently breast-fed, 18 per cent. only were healthy. As the summer was a cool one the relation of the temperature of the house to infant diarrhea could not be studied. Rohmer believes that the house itself is not most important, but rather the fact of how the house is used and how the baby is cared for.

Epstein<sup>134</sup> considers as still unsettled the question as to the cause of the action of summer heat; he believes that a high summer temperature is only one factor together with a number of other causes.

#### NOTES ON NUTRITIONAL DISTURBANCES

132. Czerny: *Jahrb. f. Kinderh.*, 1914, lxxx, 601.

133. Schloss: *Arch. Pediat.*, 1914, xxxi, 924.

134. Knox and Tracy: *AM. JOUR. DIS. CHILD.*, 1914, vii, 409.

135. Holt: *Arch. Pediat.*, 1914, xxxi, 455.

136. Holt, Courtney and Fales: *AM. JOUR. DIS. CHILD.*, 1915, ix, 213.

137. Finkelstein: *Ztschr. f. ärztl. Fortbild.*, 1914, xi, 101.

138. Bernard: Dissertation, Leipzig, 1913; *Ztschr. f. Kinderh. (ref.)*, 1914, viii, 127.

139. Hess: *Jour. Am. Med. Assn.*, 1914, lxii, 452.

Czerny<sup>132</sup> has studied the heart findings in infants with acute nutritional disturbances. A phenomenon which has been much discussed is the fact that before death in certain cases only one heart tone is heard. Czerny has always maintained that this tone is the first.

Among 195 cases of infants with nutritional disturbances varying from the mild to the severe type, Schloss<sup>133</sup> found twenty-seven cases with sugar in the urine. This sugar was usually galactose or dextrose. A hyperglycemia accompanied the melituria in most of the cases.

Knox and Tracy<sup>134</sup> have determined the excretion of phosphates in the urine of infants on various forms of feeding, and in the course of nutritional disturbances. They conclude that deductions as to the

nature and severity of such disturbances cannot be drawn merely from the amount of urinary phosphorus present.

The chemical analyses of the stools of infants with disturbances of nutrition, as well as those of normal infants, have been made by Holt,<sup>135</sup> and by Holt, Courtney and Fales.<sup>136</sup> Loose stools contained from about 100 to 200 c.c. of water per day, very loose stools over 200 c.c. The fat in very loose stools was about two and a half times that in normal stools; 64 per cent. of the fat was neutral fat in loose stools as compared with 39 per cent. in normal stools. About two and a half times as much protein was lost daily in loose stools as in normal. Of the salt elements the chlorin, potassium and sodium were much higher in proportion in the former than in the latter; 84 per cent of the total intake of ash was lost in loose stools, as compared with 40 per cent. in normal stools. The latter striking condition is commented on by the authors as giving suggestions for treatment.

#### *Alimentary Intoxication*

Finkelstein,<sup>137</sup> in a summary of his teachings with regard to the various disturbances of nutrition in infancy, states his belief that both decomposition and intoxication are due to disturbances in the metabolism of water. In the treatment the attempt must be made to stop the loss of water, and to favor a new storing up of water.

Bernard<sup>138</sup> found that an increase in the refractometric value of the blood is the rule in intoxication. He believes that this is due to an excretion of water in excess of the excretion of salt.

In severe gastro-intestinal disturbances of infants, especially in intoxication, Hless<sup>139</sup> advises the drop method of giving fluid by mouth, as aiding the administration of the large amount of water necessary in this condition. The apparatus used is similar to that in common use in the instillation of liquid into the rectum, except that a rubber nipple with a small hole is substituted for the hard rubber rectal tip. The flow from the nipple can be so adjusted that the child receives from 25 to 30 drops per minute. The infant is encouraged to suck at the nipple the greater part of the day. Water or hypotonic salt solution may be given.

#### LACTIC ACID BACILLI

140. Berry: Arch. Pediat., 1914, xxxi, 525.

141. Bendick: Jour. Am. Med. Assn., 1915, lxiv, 809.

142. Miscellany: Jour. Am. Med. Assn., 1914, lxii, 1835.

Berry<sup>140</sup> has used cultures of lactic acid bacilli in twenty-four cases of acute intestinal indigestion characterized by slight fever, vomiting and liquid stools. Some of the patients were treated simply by the administration of the bacilli; others were treated by change

in diet, and medicines in addition. He concludes that the best results were obtained when the tablets were used together with a proper change in the diet and an initial dose of castor oil. The bacilli were administered in the commercial tablets, one tablet four times daily, or in severe cases one tablet every three hours. The classification of such cases as those treated as cases of putrefactive fermentation is at variance with most theories in regard to the etiology of this type of dyspepsia.

The commercial preparations of the *B. bulgaricus* have been studied by Bendick.<sup>141</sup> He has found many specimens sterile on culture; the majority show but a small fraction of the number of living organisms represented by the manufacturer. A broth culture is the most active form of preparation. He recommends that preparations should be marked with the date of manufacture, and should always be kept in the ice-box.

A bulletin of the Department of Agriculture<sup>142</sup> discusses preparations of lactic acid bacilli. The most successful commercial preparations are the liquid forms, but dry forms are more convenient for transportation. A method devised by the Department of Agriculture consists in freezing cultures and then drying them over sulphuric acid.

#### GASTRIC DIGESTION OF INFANTS

144. Hahn: AM. JOUR. DIS. CHILD., 1914, vii, 305.

145. Schackwitz: Monatschr. f. Kinderh., 1914, xiii, 73.

146. Davidsohn: Monatschr. f. Kinderh., 1914, xiii, 182.

147. Aron: Jahrb. f. Kinderh., 1914, lxxix, 288.

148. Huenkens: Ztschr. f. Kinderh., 1914, xi, 297.

149. Ladd: Boston Med. and Surg. Jour., 1914, clxx, 518.

Many publications this year have been on the subject of the concentration of hydrochloric acid in the infant's stomach, and of the possibility of peptic digestion.

Hahn<sup>144</sup> reviews some of the previous work on this subject. Pepsin is activated in the stomach by a certain concentration of hydrochloric acid. The concentration of acid depends on the concentration of dissociated hydrogen ions; this cannot be determined accurately by titration. The methods of determination used by Michaelis and Davidsohn, the indicator and electrometric methods, are reliable. The concentration of hydrogen ions is expressed by the symbol (H), in gram ions. It has become customary to abbreviate the small decimal fractions used by means of a negative coefficient of 10; for instance  $10^{-1} = 0.1$ ;  $10^{-2} = 0.01$ ;  $10^{-5} = 0.00001$ , etc. The optimum (H) for pepsin digestion is  $1.6 \times 10^{-2}$ , while at (H)  $1.0 \times 10^{-5}$  pepsin is inert. The latter is, however, the optimum reaction for rennet and gastric lipase. Hahn has found the concentration of  $1.0 \times 10^{-5}$  quite constantly in the stomach contents of artificially fed infants at the height of

digestion. Determinations were made on ninety-four specimens from thirty-seven infants on artificial feeding (one-third cream-milk and two-thirds milk). The stomach contents for examination were removed by catheter as completely as possible, at the height of digestion.

Schackwitz<sup>145</sup> considers that the examinations previously made by Davidsohn and others have been too few to prove that the concentration of hydrochloric acid is insufficient for peptic digestion in the infant's stomach. He agrees that the physicochemical method of determination is the only accurate method; and has used this method in 137 examinations of the stomach contents of sixty infants. He finds the concentration to vary between very wide limits, so that he cannot agree with Davidsohn that the low concentration  $(H) = 1.0 \times 10^{-5}$  is constant in infants.

Davidsohn<sup>146</sup> responds by calling attention to the work of Hahn,<sup>144</sup> confirming his own earlier findings. He explains the difference in results by the fact that while he and Hahn regularly removed for examination all of the stomach contents obtainable, Schackwitz removed only 1 or 2 c.c. As the degree of acidity may differ widely in different regions of the stomach, this method may lead to error.

Aron<sup>147</sup> has suggested that in explaining the low concentration of acid found in the infant's stomach we must consider whether there is an insufficient secretion by the stomach, or whether the acid is not combined with the milk. In experiments to test the power of cow's milk and of human milk to bind acid, he has found that cow's milk binds much more acid than human milk. He draws attention to the fact that Hess found free hydrochloric acid present in the stomach of a new-born child before any food was taken. Aron believes that it is chiefly the binding of acid by milk which determines the low acidity usually present in the stomach contents of the infant.

Huenekens<sup>148</sup> has studied the acidity of the gastric contents in infants and young children when meat is given. Examinations were made on five children, aged respectively  $9\frac{1}{2}$ , 13, 17 and 20 months and 5 years. Determinations of the hydrogen ion concentration according to Davidsohn were made. In each case one determination was made after a feeding with milk, and one after a meat and vegetable feeding. After the milk feeding a low degree of acidity was found for two reasons: milk has little stimulating power on acid secretion, and it binds acid to a marked degree. After the feeding with meat the acidity in the stomach contents of the infants  $9\frac{1}{2}$  and 13 months old was slight, so that no peptic digestion could occur; in the three older children, however, there was a marked increase in the concentration of acid. Huenekens concludes that without special



reason meat should not be given to children before the second half of the second year.

Ladd<sup>149</sup> has continued his studies of the motility of the infant's stomach as shown by Roentgen ray. The administration of a large amount of alkaline fluid hastens the emptying of the stomach; this was observed when from 25 to 50 per cent. of the whole feeding was lime water, or when 0.84 per cent. of sodium bicarbonate to 200 gm. of milk mixture was given.

#### PYLORIC OBSTRUCTION

150. Holt: Jour. Am. Med. Assn., 1914, lxii, 2014.
151. Reuben: Arch. Pediat., 1914, xxxi, 809.
152. Langmead: Proc. Roy. Soc. Med., 1914, vii, 93.
153. Cautley: Proc. Roy. Soc. Med., 1914, vii, 92.
154. Hess: AM. JOUR. DIS. CHILD., 1914, vii, 184.
155. Hess: Ergebn. d. inn. Med. u. Kinderh., 1914, xiii, 530.
156. Hess: AM. JOUR. DIS. CHILD., 1914, vii, 428.
157. Peiser: Monatschr. f. Kinderh., 1914, xiii, 121.
158. Reuben: Arch. Pediat., 1914, xxxi, 782.
159. Ruhräh: Am. Jour. Med. Sc., 1914, cxlvii, 474.
160. Richter: Jour. Am. Med. Assn., 1914, lxii, 353.
161. La Fétra: Arch. Pediat., 1914, xxxi, 761.
162. Downes: Jour. Am. Med. Assn., 1914, lxii, 2019.
163. McKechnie: Canad. Med. Assn. Jour., 1913, iii, 566.
164. Lewis and Grulec: Jour. Am. Med. Assn., 1915, lxiv, 410.
165. Scudder: Ann. Surg., 1914, lix, 239.
166. Lillienthal: New York Med. Jour., 1914, xcix, 723.
167. Hougardy: Ztschr. f. Kinderh. (ref.), 1914, viii, 511.
168. Liefman: Monatschr. f. Kinderh., 1914, xii, 714.
169. Oberwarth: Ztschr. f. Kinderh. (ref.), 1914, viii, 18.
170. Lichtenstein: Dissertation, Berlin, 1913; Ztschr. f. Kinderh. (ref.), 1914, viii, 232.
171. Knöpfelmacher: Ztschr. f. Kinderh. (ref.), 1914, viii, 77.

#### *Diagnosis of Hypertrophic Stenosis and Pylorospasm*

The difficulty of the differentiation of cases of pyloric obstruction into cases of pylorospasm or of organic stenosis is commented on by most of those writing this year on this puzzling subject.

Holt<sup>150</sup> has proposed to substitute for the preceding classification a division of these cases into mild and severe. He points out the fact that there has always been great difference of opinion as to the symptoms which may be considered diagnostic of pylorospasm and those diagnostic of organic stenosis. The suggestion that a palpable tumor is a sign diagnostic of stenosis has not been accepted; nor has the theory that recovery without operation necessitates the diagnosis of pylorospasm. Holt believes that a definite persistent spasm of the pylorus without stenosis has yet to be proved, though a temporary spasm may occur. The two elements of spasm and hypertrophy are in his opinion present in each case, the essential difference in the cases

being one of degree only. The term "pylorospasm" should, therefore, be dropped, as it has led to confusion, especially in regard to indications for operation. He analyzes the symptoms of pyloric obstruction on the basis of fifty-seven cases observed by him. The great majority of these infants (fifty-two) were breast-fed; forty-nine were males.

The suddenness of the onset was noted in thirty cases, in many almost the hour of the beginning of the trouble being fixed. This fact he ascribes especially to the important part played by spasm. Vomiting began in four-fifths of his cases in the third, fourth and fifth weeks. The tumor he found to be more easily palpable during or immediately after vomiting; it persisted in some cases for weeks and even months during convalescence. The general mortality in his cases was 55 per cent.; of twenty-eight patients operated on fourteen died; of twenty-nine on medical treatment seventeen died. The indications for operative treatment he believes depend on the degree of severity of the obstruction; this is shown by the continuance of vomiting and loss in weight, and by the gastric retention, measured by aspiration of the stomach three hours after a meal. Roentgenoscopy he has found to be misleading. In the medical treatment he advises lavage twice daily, and careful feeding with a breast-milk not rich in fat; from 1 to 3 ounces of milk every three to four hours are usually given. After operation hypodermoclysis of normal saline solution with 4 per cent. dextrose is useful. Feeding with breast-milk should be begun after four hours; at first 2 drams every two hours are given; later the amount is gradually increased.

Holt's suggestion that the cases should be classified as mild or severe is considered very useful by Reuben,<sup>151</sup> as he believes that the treatment depends on the severity of the case. In his opinion, however, two distinct types of pyloric obstruction occur, the spasmodic and hypertrophic, although their differentiation is not important for treatment. In proof of this fact he states that a few of the cases which during life have shown all the symptoms of pyloric stenosis, have presented at necropsy a perfectly normal pylorus. Speaking for spasm are a neuropathic history, presence of bile in the vomitus, intermittence of the symptoms, sudden and spontaneous cure, absence of palpable tumor, or, if a tumor is present, its variation in size and shape. Reuben uses Hess' duodenal tube as an aid to diagnosis; he has found in spasm a resistance at the same point, which is felt to relax suddenly. Failure to pass the catheter after repeated attempts means a marked stenosis; a mild degree of stenosis cannot be distinguished from spasm. He considers that operation is contraindicated when the duodenal catheter can be passed.

In the discussion of a case reported by Langmead,<sup>152</sup> where the presence of vomiting, visible peristalsis and a palpable pylorus were sufficient in his opinion to show that a true stenosis existed, Cautley<sup>153</sup> expressed his belief that these symptoms were not definite evidence that a hypertrophic stenosis was present. Hess<sup>154</sup> remarks on the great difficulty found by all writers on the subject in diagnosis of pylorospasm from organic stenosis or simple vomiting. He uses as a test the passage of a No. 15 (F.) catheter into the duodenum; and in all cases in which this is possible, assumes that organic stenosis is so slight that it can be disregarded from a clinical point of view. Elsewhere<sup>155</sup> he remarks that failure to pass the catheter after repeated attempts does not absolutely exclude spasm; in two or three cases of spasm he has been unable to enter the duodenum. As an aid to passing the catheter into the duodenum in cases of spasm he advises<sup>156</sup> the giving of a little water through the tube into the stomach, after which the pylorus may frequently be passed. He has reported twenty cases of pylorospasm. In not one of these was a palpable tumor present, and he believes that tumor has never been noticed where hypertrophy was not found. He calls attention to the fact that pharyngospasm and cardiospasm are frequently associated with spasm of the pylorus. Visible peristalsis, he believes, is not necessarily a sign of organic stenosis, or even of pylorospasm; he has noticed it in cases in which neither was present.

Peiser,<sup>157</sup> in his use of Hess' duodenal catheter, has found difficulty in proving that the duodenum has been entered, and considers that the successful passage of the tube does not always contraindicate operation. In disagreement with Hess' statement that palpable tumor of the pylorus is associated only with hypertrophic stenosis, Reuben<sup>158</sup> reports a case which he diagnosed as pylorospasm, in which the duodenal catheter was passed and recovery later occurred though a palpable tumor was noticed; and Liefman,<sup>159</sup> among forty-six cases of pyloric spasm, noted a tumor in six cases.

Ruhräh<sup>159</sup> believes that a change in the size of the tumor under the palpating finger is a sign that the obstruction is spasmodic, or at any rate that spasm is the most important element. He advises operation as early as possible in cases of hypertrophic stenosis.

One can but agree with Holt that there is as yet no agreement in regard to the essential diagnostic signs and symptoms of spasm and hypertrophic stenosis.

#### *Hypertrophic Stenosis and Operative Treatment.*

Richter,<sup>160</sup> however, believes that the cases can be distinguished after a long enough period of observation, and that borderline cases do not occur. Of the twenty-two cases in which the author operated

(eleven having been previously reported) nineteen were organic stenosis, three pyloric spasm. Among his cases also, boys were in the majority; all were first-born except one. The onset of vomiting was in the second or third week and was sudden. He considers the Roentgen-ray examination misleading, as the entrance of bismuth into the intestine does not speak against hypertrophic stenosis. The mortality of his cases was very low, being 13 per cent. The eighteen children who recovered developed normally.

La Fétra,<sup>161</sup> too, states that he has found the Roentgen ray misleading and unessential in the diagnosis of pyloric stenosis.

Downes<sup>162</sup> considers that operation is indicated whenever a diagnosis of hypertrophic stenosis has been made; but operation should not be performed in cases of pyloric spasm.

According to MacKechnie,<sup>163</sup> the two conditions of spasm and organic stenosis are distinct, but an absolute diagnosis can not always be made by palpation; therefore he advises an operation in cases with marked decrease in weight. He reports six cases treated surgically.

Lewis and Grulee<sup>164</sup> report the pathologic findings at the pylorus in an infant who died of pneumonia eight months after a successful operation. An enlargement at the pylorus was found of approximately the same size and consistency as of that seen at operation, indicating that no change had occurred in the tumor. They believe that gastro-enterostomy is well borne by infants if performed rapidly and without trauma. Among five patients operated on there were no deaths.

Scudder<sup>165</sup> reports seventeen operative cases, nine of which had been reported before. There were three deaths, making a mortality of 17 per cent. A table shows the normal development of those who recovered, one having been observed for eight years. Roentgen examination in these children showed that the food continued to pass through the operative opening.

Lillienthal<sup>166</sup> and Hougardy<sup>167</sup> have reported cases of stenosis with recovery after operation.

### *Pylorospasm*

Hess<sup>154</sup> has reported twenty cases of spasm. He has described<sup>156</sup> a duodenal catheter furnished near its tip with a small collapsible balloon, which may be inflated with air after the introduction of the catheter into the duodenum, thus effecting the retention in place of the catheter for as long as twenty-four hours. He has used this catheter in a few mild cases of spasm for duodenal feeding; he has not yet made enough experiments with pronounced cases of pylorospasm to be able to draw conclusions.

Liefman<sup>168</sup> has studied the symptoms and history of forty-six cases of pyloric spasm and six cases of habitual vomiting occurring during three years in the Dresden Säuglingsheim. The mortality was 10.8 per cent. Forty per cent. of the cases were among girls; only fifteen patients were breast-fed; twenty-eight were first-born children. The onset was from the first to the sixth week, twelve cases beginning in the third week. That a pyloric tumor was present in six cases has been mentioned. In the latter history neuropathic symptoms were noted only in one-half the cases. The general development was normal.

Oberwarth<sup>169</sup> reports twenty cases of spasm; all the patients recovered on medical treatment. He considers important the regular rectal instillation of 200 gm. of breast-milk daily.

Ruhräh<sup>159</sup> in cases of pylorospasm advises stomach washing several times daily, using 0.8 per cent. sodium bicarbonate solution if much mucus is present. He considers atropin the best medical treatment.

Lichtenstein<sup>170</sup> reports fifteen cases of pylorospasm in infants. Knöpfelmacher<sup>171</sup> reports a case of pylorospasm favorably influenced by papaverin.

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## SOME STUDIES ON SUGAR IN INFANT FEEDING \*

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Some years ago Finkelstein<sup>1</sup> caught the attention of the world by formulating a new conception of the underlying causes of what were then considered diseases of gastro-intestinal origin. He described them as purely nutritional disturbances, divorced them from any relationship with the bacterial invaders of the intestine, and laid the blame of their genesis on an element of diet that had heretofore been considered innocuous, namely, the sugar. Especially did he attribute that serious, acute form of infantile disease accompanied by stupor, mellituria, and fever to the sugars. The last two symptoms were, he taught, directly and proportionately due to its presence in the food. Later, he implicated the mineral salts of cows' milk, still later prepared his celebrated "Eiweissmilch" and offered it as a remedial food for sugar intoxications, apparently overlooking the fact that as this mixture contained 1.5 per cent. of the deadly lactose its use in practice contradicted his theory. Lactose was especially the sugar he feared, so much so that he stated that even minute doses of milk containing its natural carbohydrate were damaging. Babies were injured with lactose, dextrose, lactose salt mixtures, and dextrose alkali or lactose alkali mixtures, given in isotonic, hypertonic, or hypotonic proportions. The injury was considered always to express itself in mellituria and fever, and F. M. Schapps, Leopold and Von Reuss were one in thinking with Finkelstein that lactose was "exquisitely pyrogenic." This point was emphasized by the findings of Finkelstein and Meyer that 3 gm. of sodium chlorid in 100 c.c. of water given by mouth could produce fever in many healthy infants, while if nutritional disorders were present 1 gm. sufficed to produce pyrexia.

In the next few years the men of this school decided that sugar damage was not alone a simple sugar injury, but made itself felt as the result of the previous or coincident action of salts in improper

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proportions in the food, the presence of the chlorin ion combination with sodium being especially blamed. About four years ago the idea that fermentation of sugar in the intestine played some rôle in these disorders began to be emphasized in Finkelstein's writings, and Finkelstein and Meyer laid greater stress on the fermentation of lactose in the intestine and less on the toxicity of sugar acting parenterally. They even admitted that human milk, which of course is high in lactose, may be the optimum food for certain of the cases that occurred under their classification of intoxication, apparently thus abandoning the view that milk sugar is a fatal poison in such disorders. This inference from the writings of Finkelstein is confirmed by his pupil Schultz, whose experiments did not bear out the pyrogenic or intoxicating action of the sugars. The latest position of Finkelstein's school seems to be that fermenting lactose injures the permeability of the intestinal wall, permits the absorption of salts in abnormal kind or quantity, and that these salts, either alone or in combination with the sugar, produce the poisoning which is evidenced by the glycosuria.

As to fever, there was some reason to believe that when it occurs it is the result of tissue damage such as is often seen following injections of sterile water or salt solution when they break up the erythrocytes, analogous to the fever not at all infrequently seen in childhood that follows extensive bruising or the production of hematomata.

The most convincing work among the group of men that oppose the Finkelstein-Langstein view was done by Allen working in Rose-nau's laboratory. In a long series of experiments with animals in the nursing stage the effects of sugars were tested when given both by mouth and subcutaneously. Experimental animals were used and the experiments ingeniously devised to meet all objections. The animals were given large doses and small doses, some were given repeated injections and some single large doses. Those animals which received their sugars by mouth, especially lactose, showed as effects vomiting and diarrhea, which undoubtedly were due to the fermentation of the sugars in the intestine. In no one of the animals was there any sign or symptom of an intoxicating action of sugar, nor was Allen able to produce any symptoms at all approaching the clinical picture of the sugar intoxications as outlined by the Germans. On the contrary, in spite of glycosuria, which occurred in all experimental animals, he was able to see that subcutaneous injections of glucose were very definitely beneficial to his kittens and puppies, especially to one group that was weaned early and doing very badly. This seems a more rational finding than the view that implicates sugar as a poison to metabolism, as every one has seen the apparent benefit of glucose injections in the case of very sick babies.

The study of the literature would make it seem that the origin of the idea of sugar damage went back to Grosz, and was later elaborated by Langstein and Steinitz in a paper, "Lactase und Zucker Ausscheidung," published in 1906, which seems to have turned Finkelstein's interest toward the sugars as agents of possible damage in infantile nutritional disturbances. These authors in fourteen cases of severe gastro-intestinal disorders proved to their own satisfaction that a part at least of the sugar excreted into the urine was lactose. In five cases they found a second sugar which they believed to be galactose. They conclude that there can be no doubt that infants with severe gastro-intestinal disease excrete milk sugar, and its split-off product, galactose, in the urine, and that this excretion is independent of the excretion of lactase in the stool. They further say that in severe cases of gastro-intestinal disease only part of the milk sugar is split by lactase into dextrose and galactose. These are then burned in the organism or the galactose is excreted if the oxidizing power of the tissues has suffered. The second portion is absorbed unsplit and excreted as lactose in the urine. They admit that the largest proportion may be split by fermentation in the intestine and may be lost to the organism.

The views of Kendall are that lactose, far from being an injurious food, is of essential importance in so maintaining the flora of the intestine that the fermentative processes will always be slightly dominant, and will prevent the putrefactive action on protein which produces soluble toxin of undoubted damage to the general metabolism. The work of Allen and the paper of Kendall are both worthy of very close study by any one who is interested in the subject. Raphael showed that many patients assimilate large doses of sugar better than small ones. Schlessinger says that the appearance of the traces of sugar in the urine are no indication that the sugar tolerance of the body has been passed. Naunyn says that small traces of sugar may be ignored in animals who may show a slight glycosuria, with small doses and none with large. Platenze says sugar is often to be found in urine of babies who show no sign of intoxication and who seem perfectly well.

The dosage usually given for pure dextrose as one that will exceed the sugar tolerance is between 100 and 250 gm. for the adult, but many individuals can assimilate more. After the subcutaneous injection of 100 gm. of glucose, glycosuria may last as long as eight hours. The single dose maximum seems to be from 2 to 4 gm. per kilo, by mouth, 10 gm. per kilo per day, and subcutaneously 1 to 1.5 gm. per kilo per dose.

The presence of traces or of even considerable amounts of reducing bodies in the urine does not mean that sugar is present. Schultz says that a reduction test which will exclusively demonstrate the presence

of sugar is not known, and further, reducing substances such as uric acid, creatinin, albumen, coloring matter, acetone, glycuronic acid, all or any may be present. Fluckiger reports the presence in normal adult urines of non-fermentable reducing bodies which produce osazones of a value equal to 1/1500 to 1/2500 gm. of grape sugar in the twenty-four hours. Salkowski put it at 0.4 gm., Monk at 0.3 gm., and other observers at variable points. Creatinin has especially been dealt with by Sedgwick, Steinitz, Fluckiger, Amberg and Morris, so that it is clear that in infants' urines there may be considerable reducing power due to bodies other than carbohydrates, a fact well substantiated for the normal urine of adults.

This fact, together with the report by the Finkelstein school of the frequent presence of sugars in the urines of infants suffering with a less severe nutritional disturbance, made it seem desirable to test the urine of a group of infants in the Boston Infants' Hospital, who were suffering from what would be known in Europe as "balance disturbance," but which in the nomenclature of the Boston school is called "chronic indigestion." There were eighteen of these babies investigated; none of them were of the premature type such as Aschenheim found to have intestines more permeable to sugar than those of older nurslings. The first tests were all made while the children were receiving what was considered a normal amount of sugar advisable for their individual peculiarities. Later, attempts were made on a number of the cases to find the limit of physiologic tolerance for the sugars. The reagent used in the determinations was one recommended by Folin as the most sensitive to reducing bodies. It was made in two solutions, of which 3.5 c.c. of each were mixed at the time of using and from 1 to 3 c.c. of the urine added after boiling the mixture. The mixture was then centrifuged. Solution 1 contained copper sulphate 10 gm., glycerin 150 c.c., and water to make 500 c.c. Solution 2 contained 500 c.c. of a 50 per cent. solution of potassium carbonate. This reagent has shown definite amounts of reducing bodies in every adult urine tested with it. This is not true of infants' urines. Twelve per cent. showed no reduction whatever, and of the remainder, 50 per cent. gave no reduction on repetition of the test after saturation with picric acid and shaking through ten minutes to remove the creatinin which is present in appreciable quantities in nearly all infants' urines, and which reduces nearly all the copper reagents especially the more delicate. In none of the urines was it possible to measure the reduction quantitatively by Benedict's solution.

The fact having been determined that there was no measurable sugar in any of the urines tested, attempts were made to pass the sugar tolerance limit of 2 to 4 gm. per kilogram of body weight without the production of a measurable glycosuria. Such attempts

have been made before and have always failed to cause a glycosuria except in those cases of deep intoxication such as were studied by Finkelstein and his pupils.

A summary of the work done in this investigation is as follows: Patients observed, 18; samples of urines tested, 105; number of tests made, 235; signs double + and triple + are used as follows: + indicates on the addition of the urine to the heated reagent a few grains of copper oxid; ++ indicates that on centrifuging definite layer of copper oxid forms in the bottom of the tube; +++ that there is a visible reduction in the tube before centrifuging. Sixteen of the eighteen patients showed reducing bodies in some tests before the treatment with picric acid. Eight showed a loss of reducing power after shaking with picric acid. Three of the patients (++++) showed appreciable amounts of reduction constantly in all samples of urine after the picric acid treatment. One of these had an eczema corresponding in type to the exudative diathesis of the Czerny school, but in spite of the fact that this patient received as much as 120 gm. of lactose, 15 per cent. of his intake per day while he was receiving 4 per cent. of fat at the same time, there was never enough sugar in the urine to be assured by any of the usual quantitative methods and coincidentally the skin condition improved steadily under local treatment. The other two patients of this group were suffering from rather extreme malnutrition. Of the 105 samples of urine, 58 showed reducing powers to our solution before shaking with picric acid. Of these 58, 27 lost their reducing power after such treatment. Of the eighteen patients, excepting the three referred to above, none showed reducing bodies every day, and in no instance did there seem to be any relation between the amounts of sugar ingested and the presence of these bodies as they were found in the urine with minimum intake, and were frequently absent following the highest ingestion.

The clinical results in these cases in which an effort was made to surpass the supposed limits of sugar tolerance were very interesting. Not knowing how severe the symptoms of intolerance might prove to be, we did not wish to give large doses of sugar suddenly, but adopted the method of a gradual increase in the amount of sugar given. The percentage of sugar in the food was increased at the rate of 0.5 per cent. a day until symptoms of intolerance developed. Lactose only was used in nine cases, dextrimaltose only in 1 case, and the tolerance for both lactose and dextrimaltose was tested in six cases.

None of the cases tested were of the severest type of malnutrition. One or two of the patients were babies having no gastro-intestinal disturbance. One presented a case of congenital obliteration of the bile ducts. The majority were babies who had presented difficult

feeding cases in the Out-Patient Clinic, and had been sent in to the hospital to be straightened out. None showed any marked intolerance for any of the food elements. The majority were comparatively mild cases of fat intolerance, showing indigestion and excessive fat in the stools when the fat was increased. No case known to have a marked intolerance of carbohydrate was tried.

Symptoms of intolerance developed eventually in twelve of the sixteen cases. Three patients were taken home, and one patient died, before the experiment was completed.

TABLE 1.—MAXIMUM SUGAR TAKEN WITHOUT SYMPTOMS

Case	Percent. in Food	Gm. in 24 Hours	Gm. in 24 Hrs. per Kg. of Body Weight	Gm. in a Single Feeding per kg. of Body Weight
1	Lactose, 9.5 .....	91	9	2.25
2	Lactose, 7 .....	83	20	3.00
3	Lactose, 14.5 .....	169	31	4.75
4	Lactose, 14 .....	119	40	4.00
5	Lactose, 11.5 .....	134	28	4.00
6	Lactose, 15.5 .....	144	32	4.40
7	Lactose, 8.5 .....	79	18	3.00
7	Maltose, 9.5 .....	91	20	3.00
8	Lactose, 15.5 .....	168	27	4.50
9	Lactose, 5 .....	53	10	2.00
9	Maltose, 12.5 .....	158	27	4.50
10	Lactose, 7.5 .....	67	24	2.00
11	Lactose, 8.5 .....	100	20	3.00
11	Maltose, 8.5 .....	100	20	3.00
12	Lactose, 12 .....	160	17	3.00
13	Maltose, 11.5 .....	119	33	3.10
14	Lactose, 10.5 .....	140	30	3.00
14	Maltose, 18.5 .....	170	54	5.40
15	Lactose, 11.5 .....	150	18	3.00
15	Maltose, 17.5 .....	225	27	4.50
16	Lactose, 13 .....	146	22	3.10
16	Maltose, 18 .....	182	30	4.00

The symptoms of intolerance were very constant. The first symptom, showing the coming on of intolerance, was marked irritation of the skin of the buttocks, in spite of the most careful nursing. The symptoms which soon followed were loose green movements, usually about five or six daily, distention of the abdomen with gas, eructations of gas, and vomiting. Loss of weight was slight; on the development of distinct signs of intolerance, the sugar was at once cut down. In no case were seen any toxic symptoms, or any signs of sugar intoxication, or any fever, except that one case developed fever at about the

time of the other signs of sugar intolerance, but at the same time this baby had an acute otitis media. The symptoms of sugar intolerance, therefore, judging from this series of cases, are in no way suggestive of intoxication, but are suggestive only of a fermental process localized within the intestinal canal.

The amount of carbohydrate taken without intolerance was surprising. The quantities of sugar given to the several cases are shown in the tables. Table 1 shows the maximum quantities of sugar taken

TABLE 2.—AMOUNT OF SUGAR ON WHICH SYMPTOMS OF INTOLERANCE DEVELOPED

Case	Percent. in Food	Gm. in 24 Hours	Gm. in 24 Hrs. per Kg. of Body Weight	Gm. in a Single Feeding per kg. of Body Weight
1 *	.....	...	...	...
2 †	.....	...	...	...
3	Lactose, 15 .....	141	26	4.0
4	Lactose, 14.5 .....	113	40	4.0
5	Lactose, 12 .....	144	30	4.25
6	Lactose, 16 .....	146	32	4.40
7	Lactose, 9 .....	76	17	3.00
7	Maltose, 10 .....	105	32	3.20
8 †	.....	...	...	...
9	Lactose, 6 .....	53	10	2.00
9	Maltose, 13 .....	150	26	4.60
10	Lactose, 8 .....	72	26	2.00
11	Lactose, 9 .....	105	20	3.00
11	Maltose, 9 .....	105	20	3.00
12	Lactose, 12.5 .....	172	18	3.00
13 †	.....	...	...	...
14	Lactose, 11 .....	145	30	3.00
14	Maltose, 19 .....	170	55	5.40
15	Lactose, 12 .....	152	18	3.00
15	Maltose, 18 .....	227	19	4.50
16	Lactose, 13.5 .....	148	22	3.10
16	Maltose, 18.5 .....	186	31	4.00

\* Patient died before intolerance developed.

† Patient discharged before intolerance developed.

without intolerance. These quantities were in general far above the supposed limit of 10 gm. daily per kilogram of body weight. The percentage of sugar taken without intolerance varied from 5 to 18.5 per cent., the grams in twenty-four hours varied from 53 to 225, the grams daily per kilogram of body weight varied from 9 to 54, and the grams of sugar at a feeding per kilogram of body weight varied from 2 to 5.40. The quantities on which intolerance eventually developed were slightly higher, and are shown in Table 2. Only one baby in

TABLE 3.—PERIODS OF INCREASED SUGAR, QUANTITY OF SUGAR TAKEN, AND GAIN OR LOSS IN BODY WEIGHT

Case	Food	Period of Increased Sugar (Days)	Percent. of Sugar in Food at Beginning of Period	Percent. of Sugar in Food at End of Period	Sugar in 24 Hours per kg. of Body Weight at Beginning of Period gm.	Sugar in 24 Hours per kg. of Body Weight at End of Period gm.	Gain or Loss in Body Weight During Period gm.	Average Daily Gain or Loss in Body Weight Period gm.
1	Lactose .....	8	9.5	9.5	9	9	—	—63
2	Lactose .....	13	7.0	7.0	20	20	+	+22
3	Lactose .....	20	7.0	15.0	16	31	+	+36
4	Lactose .....	18	7.0	14.5	22	40	+	+7
5	Lactose .....	18	6.5	12.0	18	28	+	+13
6	Lactose .....	20	6.5	16.0	14	32	+	+33
7	Lactose .....	8	5.5	9.0	13	18	+	+27
7	Maltose .....	10	6.0	10.0	14	20	+	+26
8	Lactose .....	19	6.5	15.5	12	27	+	+52
9	Maltose .....	16	6.0	13.0	14	27	+	+31
10	Lactose .....	4	6.5	8.0	21	26	+	+30
11	Lactose .....	7	7.0	9.0	16	20	+	+4
11	Maltose .....	7	7.0	9.0	16	20	+	+13
12	Lactose .....	13	6.5	12.5	9	18	+	+16
13	Lactose .....	20	6.5	16.5	11	33	+	+50
14	Lactose .....	7	7.0	10.5	20	30	+	+27
14	Maltose .....	22	7.0	18.5	20	55	+	+30
15	Lactose .....	10	6.5	11.5	9	18	+	+22
15	Maltose .....	22	6.5	17.5	9	28	+	+36
16	Lactose .....	13	6.5	13.0	14	28	+	+19
16	Maltose .....	22	6.5	18.0	14	36	+	+26



the series showed inability to take more than 7 per cent. of sugar, or more than 10 gm. per kilogram of body weight in twenty-four hours.

In the six cases in which the comparative tolerance for maltose and lactose was tried, it was found to be about the same in two cases, but distinctly higher for maltose than for lactose in the other four cases. In no case was there the slightest evidence of any relation between the amount of sugar given and the presence of a positive sugar test in the urine. The sugar was just as likely to be absent as present in cases taking a maximum of sugar, or in cases showing symptoms of intolerance. The three cases showing the constant presence of sugar, showed the same reaction irrespective of the amount of sugar given. The other cases show positive and negative urinary tests at all stages. The last three cases, numbered 14, 15 and 16, showed sugar more often present with maltose than with lactose. Whether this is the rule requires further observation.

The effect of the increased quantity of sugar on the weight curves of the babies was most surprising, and is shown in Table 3. The majority of the cases not only gained weight, but gained weight very rapidly during the period of sugar increase. Also the gain, while less rapid after sugar intolerance developed and the sugar was cut down, was in all cases maintained. In some instances the gain was really enormous. Patients 8 and 13, both on lactose, gained 1,000 gm. in twenty days. Only one case, which afterward proved to be tuberculous, failed to gain. Excluding this case, the average daily gain for the whole series during the sugar period was 26 gm.

It seems to us that the idea of sugar injuries and sugar intoxication has possibly kept us from the use of large amounts of soluble carbohydrate in certain cases, particularly those unable to take a quantity of fat sufficient to meet their nutritive requirements. That many such babies have intolerance of sugar is indoubtedly true. But the danger of pushing the sugar to the limit of tolerance we believe to have been exaggerated. The signs of sugar indigestion are distinct and easily recognized, and do not appear to be in any way serious. In many cases great benefit appears to be obtainable by greatly increasing the carbohydrate content of the food, and therefore this proceeding may prove a valuable addition to our stock of resources in dealing with difficult feeding cases.

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## PYLORIC HYPERTROPHY IN NEW-BORN INFANTS

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During the last ten or fifteen years, in which hypertrophic pyloric stenosis and pylorospasm in infants have been the objects of absorbing interest, the prevailing tendency has been to draw well-defined clinical pictures of these two affections, and to distinguish them sharply from normal conditions, as well as from each other. With regard to the latter distinction, the chief object has been to define the operative indication; we have now come to understand that this end is not always attainable, and that difficult borderline cases form a large proportion of the total. As a matter of fact, the absence of any sharp dividing line was more than suspected ten years ago by Ibrahim,<sup>1</sup> and has recently been reaffirmed by Holt.<sup>2</sup> Careful study of the best contributions to the subject conveys the impression that this attitude of uncertainty pervades most of the literature; only the surgeons, possessed of a more limited view, seem to maintain rather positive opinions, where the pediatricists are vexed with doubts.

With the aid of certain postmortem material that has recently been at my disposal, I shall endeavor to show that even the first proposition, namely, the diagnosis between pyloric hypertrophy and presumably normal conditions, is beset with difficulties, and that, as a consequence, the distinction between spasm and true organic obstruction is likely to remain, in many cases, a matter of great uncertainty unless new diagnostic methods are brought to our aid.

The following new-born infants were examined:

CASE 1 (No. 15887).—Baby S., premature, died in the third week, of atelectasis. The pylorus forms an obviously thickened mass, its walls being about 4 mm. in diameter, but the lumen appears to be fully normal. The pylorus as a whole projects into the duodenal canal very much in the manner of a cervix uteri, and as described in cases of true pyloric hypertrophy.

CASE 2 (No. 15894).—Baby S., died on the fifth day, of hemophilia of unknown origin. The same condition of the pylorus is found, the lumen of the organ measures 6 to 7 mm. in diameter.

CASE 3 (No. 16149).—Baby S., died on the fifth day of multiple hemorrhages. The pylorus presents the same thickening of the walls, and projection into the duodenum, with a lumen of 8 to 9 mm.

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1. Ibrahim: *Die angeborene Pylorusstenose im Säuglingsalter*, 1905.

2. Holt: *Medical Versus Surgical Treatment of Pyloric Stenosis in Infancy*, Jour. Am. Med. Assn., June 17, 1914, p. 2014.

CASE 4 (No. 16148).—Baby C., died in the third week, of congenital atresia of the bile ducts. Pylorus exactly as noted in Case 3.

By way of comparison, I give two autopsies of older infants.

CASE 5 (No. 15818).—Frances K., died at 3 months of meningitis. The pylorus is little, if at all, thicker than the duodenum, and does not project into it; the pyloric wall is of about normal thickness.

CASE 6 (No. 16364).—Frank E. died in the fourth month, of an exceptionally severe purulent meningitis. There is in this case a slight thickening of the pyloric wall, but less marked than in any one of the four new-born infants.

To these I may add a previously<sup>3</sup> reported control case:

CASE 7.—Died in the eighth week, of gastro-enteritis. Pyloric wall is not at all thickened, measuring 2.5 mm. in diameter; the viscus does not project into the duodenum.

#### SUMMARY

In summarizing the above cases, I wish, in the first place, to call attention to the substantial uniformity of conditions in the first four cases, which were consecutive, not selected, and in which the pyloric findings were accidental, and not sought for. The conditions in any one of these four infants might have led to pyloric spasm, which, according to Ibrahim,<sup>1</sup> is a probable causative factor in the development of true organic obstruction.

In the middle period of infancy, we have plainly a different state of affairs in the normal subject. There is usually no thickening, or it is, at any rate, very slight, as in Case 6. As far as can be determined from so small a material, a retrogressive change normally takes place between the third week and the third month, in the course of which the very perceptible thickening of the pylorus gives way to a condition in which the borders of that organ are macroscopically almost undistinguishable.

The first group of cases presented no symptoms of spasm or obstruction. The latter was plainly not present, and the former does not occur, even in predisposed cases, until the third week of life. The stated findings do not, therefore, conflict with our clinical observations. The question of a postmortem contracture, long since thrashed out, is here refuted by the conditions noted in the second group; also in a few of these cases by the performance of the autopsy after rigor mortis had disappeared. As in obstructive hypertrophy, so in these cases, the total bulk of the viscus was greatly increased; in postmortem spasm the increased thickness would be compensated by an equivalent shortening of the organ.

The thickness of the pyloric wall in the normal infant of two months is 2 to 2.5 mm., in the new-born it is greater, 3 to 4 mm., in established hypertrophic stenosis fully 5 mm.; evidently the conditions in the new-

3. Wachenheim, F. L.: *Am. Jour. Med. Sc.*, April, 1905.

born are intermediate, and it depends on circumstances whether the normal retrogressive change takes place, or the thickening increases to such a degree as to cause obstruction. Possibly the development of the latter condition is due to hyperacidity and consequent pylorospasm, leading to hypertrophy, as is believed by some authors, but this sequence is so far purely conjectural. At any rate, the average new-born infant bears within itself the latent tendency to develop pyloric hypertrophy, and it depends on factors hitherto uncontrollable whether the stated condition develops or the pyloric wall thins out in the normal course.

Owing to the small number of cases in my series it would be presumptuous to state that the pyloric thickening in the new-born is universal; its occurrence in four consecutive cases seems to show that it is present at least in the majority, but further research along these lines is imperative, and may lead to valuable results if my observation is confirmed by other investigators. Further research may also lead to an explanation why some infants never get beyond the clinical picture of pylorospasm, whereas a considerable number go on to true organic obstruction. The working out of prophylactic measures may likewise result from further studies; in this respect the present dietetic treatment of pylorospasm possibly points the way.

I wish to thank my adjunct, Dr. B. M. Wronker, for valuable assistance.  
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## STUDIES IN BRONCHIAL GLANDS \*

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The impetus for this study of bronchial glands came from what seems to be the growing opinion that chronic adenitis of the bronchial glands is always tuberculous. This opinion may have arisen from the specialist in tuberculosis or from those examining sick children for possible tuberculosis, for by such is an examination of these glands usually made.

In order to determine the frequency of chronic adenitis of the bronchial glands in infancy and childhood, the reliability of the signs, and the possible pathology of the gland, I have examined, during the past year, all cases coming under my care, no matter for what reason. This series of cases came from three sources: from the Infants' Hospital, from a large school and from private practice. At the Infants' Hospital the patients were infants under 2 years, admitted for non-contagious medical diseases including nutritional disturbances. This gave over three hundred cases. The school is located in a healthy suburb of Boston and draws children from families of moderate circumstances and is not a tenement district. There are 700 in the school, but only 500 between 6 and 13 years of age are included in this series. The cases seen in private were in and about Boston, and were those usually seen in general practice confined to infants and children.

The means used to demonstrate enlarged glands were auscultation and percussion, the Roentgen ray being employed to confirm physical signs. By auscultation I mean determination of the sign described by D'Espine as the point on the vertebral column at which whispered voice changes from a vesicular to a bronchial character, and was given by him as taking place at the seventh cervical. In infancy it is impossible to get whispered voice, but the character of the expiration is as satisfactory, and is best heard after crying. In very few cases have I found the change as high as the seventh cervical, but commonly at the first or second dorsal, and frequently as low as the third without cause. The average height increases with age. I found no case at the seventh cervical in infancy, the average being between the second and third dorsal; at 6 years 40 per cent. had changed at the second dorsal; at 12 years 85 per cent. had changed at the second dorsal.

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\* From the Infants' Hospital, Boston.

and several cases at the seventh cervical. The sign differs in degree or rather in intensity of the bronchial character, depending on the amount of gland involvement, their size and position. Just as in lung examination it is not the harshness of the breathing but its character that counts, so in the D'Espine sign it is the point where the breathing changes from vesicular to bronchial and may be loud or distant. Hence from the foregoing I have accepted as a positive D'Espine a change in character of whispered voice or expiration at or below the third dorsal.

Percussion for glands has been very difficult, and to map out with any degree of certainty the area of dulness into cone shaped and circular areas, as described by some writers, I have found difficult. Dulness to the left of the sternum and spine is masked by the heart and great vessels. Dulness in the second interspace to the right of the sternum, and dulness to the right of the vertebral column at the level of the spine of the scapula is definite and significant and seems to agree pretty well with the intensity of the D'Espine.

The Roentgen ray was used as routine only in the hospital cases. The physical examination was made and recorded, then a roentgenogram was taken to check up the physical findings. In no case with positive signs did the roentgenogram fail to show a shadow. Enough of the cases have come to postmortem to prove the reliability of the signs and the Roentgen ray.

The bronchial glands, speaking of the various groups as if of one group, may be inflamed just as any other glands may be, and may be acute or chronic or apparently chronic from constantly draining a diseased area. There seems to be a choice of glands involved depending on the source of the infection; the glands along the trachea drain the upper regions, the hilus or tracheobronchial glands drain the lung, both sets giving positive D'Espine, the hilus glands more commonly giving dulness.

Acute adenitis of the bronchial group need give little concern, for the signs disappear rapidly after the parent disease subsides. The importance of adenitis of this group seems to me to lie with the chronic ones, or those which appear to be chronic. As I said before, there is an impression that chronic adenitis of the bronchial glands means tuberculosis. If we bear in mind that tuberculosis of infancy and childhood is primarily a chronic inflammation of the glands adjacent to the portal of entry, and that the portal of entry is most often in the lungs, then the importance of chronic hypertrophy of the bronchial glands becomes apparent. The cases entering the Infants' Hospital since July, 1914, for conditions other than acute infectious diseases, and without history of recent acute infectious disease of the air pas-

sages, showing positive D'Espine and interscapular dulness with or without lung signs, have proved to be tuberculous. I shall mention a few cases in illustration.

CASE 1.—Girl baby, 15 months old, admitted for anemia following improper diet. Examination showed dulness at the right apex, distant bronchial breathing and fine râles; right interscapular dulness, positive D'Espine, Pirquet positive.

CASE 2.—One month premature girl admitted Feb. 25, 1915, for regulation of feeding and observation to find the cause for febrile attacks recurring at intervals of three weeks. Examination showed signs at right apex, interscapular dulness and positive D'Espine. Pirquet negative February 28, positive March 25.

CASE 3.—A seven months baby seen in private with the story that it could not take the bottle; had done well for four months on the breast when breast milk gave out. It seemed willing to try the bottle, but after sucking a few times gagged and spit out the milk. Adenoids had been removed without relief. Physical examination showed dulness, bronchial breathing, fine râles at the right apex, right interscapular dulness, positive D'Espine. Stomach tube passed with difficulty. Father tuberculous.

With what certainty chronic bronchial adenitis may mean tuberculosis in infancy some cases I had seen in private practice led me to believe that it might be otherwise with older children. I have watched children for months with positive D'Espine, troublesome, dry, brassy cough to have all signs disappear after removal of adenoids. Hence, to determine the frequency of positive signs and the possibility of other sources of infection I made the second part of my series of examinations, that is, in presumably well schoolchildren. This was unsatisfactory in some respects for I was not permitted to make Pirquet tests or roentgenograms and so the cases must go without these checks. All the cases were examined in the fall of 1914, and all positive cases were reexamined during the past three weeks, or at least three months after. Out of a total of 505 children examined in the school there were 112 with positive D'Espine at or below the third dorsal. Of the positive cases 96 were at the ages of 6, 7 and 8 years from a total of 297 cases at these ages. The remaining 16 positive cases were at the ages of 9, 10, 11 and 12 years. For some reason positive D'Espine was very much more frequent in the younger half, 36 per cent. as against 8 per cent. The most common defects at the younger age were carious teeth, adenoids and tonsils and if such cases had chains of enlarged glands down the neck, showed positive D'Espine.

Most of the younger children were in good condition, might have a cough but showed no malnutrition or anemia. Some of them were undernourished and anemic, and beside a positive D'Espine showed interscapular dulness or a slightly dull apex.

The older groups, sixteen in all, gave a different picture. Ten undernourished, anemic children with interscapular dulness and dul-



ness at one apex; three no dulness but anemic and undernourished; three in good condition having carious teeth and glands in the neck; no case in either group with so-called active tuberculosis meaning active pulmonary signs.

After completing the examinations I went into the histories. The same family name often appeared, and after they were grouped according to the name frequently all the children of a family in the school appeared in my series. Among the younger half there were 27 with a history of definite exposure to tuberculosis and among these were found the cases with positive D'Espine, dulness and malnutrition. In the older half, in the 13 cases with D'Espine, dulness and malnutrition there was a history of exposure in every case. The other three showed merely a positive D'Espine without dulness or malnutrition, and gave no history of exposure.

In all these cases I did not separate the glands into groups but took the signs as they came, hoping to be able to draw some working conclusions from the results. For purposes of diagnosis I think it would be well to think of these glands as of those up and down the trachea, and of those at the root of the lungs. Inflammation of both of the sets will give positive D'Espine, dulness accompanying those at the root of the lungs, and not with glands down the trachea unless there is also consolidation at the apex of the lungs. The upper set becomes enlarged from draining the upper regions and gives a narrow chain which is sufficient to transmit the bronchial character of the sounds but does not give dulness. Hence I believe a positive D'Espine with interscapular dulness means thickening at the roots of the lungs, secondary to a process in the lungs which in infancy means tuberculosis, and, in older children, if accompanied by malnutrition and anemia, is probably tuberculosis.

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# ACUTE NONEPIDEMIC INFLAMMATION OF THE SUBLINGUAL GLANDS IN CHILDREN: AN AFFECTION OF UNKNOWN ORIGIN \*

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That the sublingual glands may be involved in epidemics of mumps, alone or in conjunction with the other salivary glands, is well known. Whenever reports of nonepidemic inflammation of the sublingual glands are made, well-defined local or combined general and local causes are given. The group of cases I wish to report does not fall into either of these categories. They are characterized, in brief, by the rapid development of a sublingual and median submental swelling, and fever, in previously healthy children; fever soon recedes whereas the swelling under the chin progresses, the overlying skin often becomes reddened, and, about the time the appearances point to the development of an abscess, the submental lesion slowly subsides.

Most of the patients presenting this condition (in all, about a dozen cases have been seen) have come under my observation in the surgical department of the Mount Sinai Hospital Dispensary in the past six years. The significance of the earlier cases was entirely overlooked, and no special attention was given to the submental swelling that was usually considered a lymphadenitis from an undiscoverable cause. Indeed, as recently as 1912, I operated upon one of these patients under the totally erroneous impression that I was dealing with a submental abscess. The description of this case and two more recent ones that could be followed carefully will sufficiently illustrate the clinical picture.

CASE 1.—A girl, 9 years old, came under my observation in April, 1912, in the Mount Sinai Hospital Dispensary, with the history of progressively increasing median submental swelling, some sublingual pain and fever, for five days. Local treatment had not been employed. There were no previous illnesses.

*Examination.*—A slightly sensitive swelling beneath the sublingual mucous membrane was found, but no focus of infection in the mouth could be discovered. The large mass below the point of the chin was brawny and tender; the overlying skin appeared adherent and was deep red.

The diagnosis of a submental abscess was made. It was determined to drain this through the mouth because the supposed abscess appeared intimately connected with the floor of the mouth. At operation the very edematous mucous membrane and submucous tissues under the tongue were incised. Dressing forceps were passed through the infiltrated submental tissues in various directions; a little clear fluid escaped, but pus was not encountered. Aspiration at several points was also negative. The wound was packed.

The postoperative course was uneventful. The submental lesion appeared unaffected by the operation; it remained unchanged in size for four days and

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then slowly receded, the overlying skin gradually assuming a violaceous hue. Nine days after the operation the submental swelling was gone, the sublingual incision healed. The patient was well when seen several months later.

CASE 2.—An obese girl aged 7 was always well except for an attack of gangrenous appendicitis with diffuse peritonitis, for which I operated in August, 1913. In February, 1914, she came under observation with a very pronounced median submental swelling of two days' duration. The child had been well since the operation; there had been no lesion of the mouth or face, no complaint of toothache. Mumps not present in any of the children in the house. Preceding the onset of the swelling there was feverishness and malaise for about twelve hours. When first noticed the submental lesion was very small and painful; it increased in size very rapidly, the mild constitutional symptoms soon disappeared. A little thickness of speech developed.

*Examination.*—The marked "double chin" effect of the submental swelling gives the child a very grotesque appearance. The brawny mass is the size of a small hen's egg and is capped by a red and glossy patch of skin. The latter is surrounded by a zone of tense, faintly bluish skin. The mass is not very sensitive. Adjoining it are a few small slightly tender lymph-nodes. The tongue is somewhat raised by the swelling on the floor of the mouth. The sublingual fold is very edematous; on either side the mucous membrane is domed to almost hemispherical proportions. These masses are slightly tender and doughy to the touch. As determined by combined palpation, the sublingual and submental swellings merge into one. There is no escape of saliva on pressure. Several reddish spots are seen in the sublingual mucous membrane. These appear to be the inflamed orifices of the sublingual ducts; the smallest probes could not be introduced into them.

Four days after the onset of the illness the child was seen again. The submental swelling was slightly larger and more tender; the sublingual tumefactions were smaller. Speech was normal. The general condition was excellent. Temperature, 99.8. White blood count, 10,200; 65 per cent. polymorphonuclears. The submental mass did not begin to recede until five days later. The overlying skin then began to assume a faintly violaceous color; the surrounding lymph-nodes were no longer palpable, and the sublingual swelling was gone. A small, rather firm submental mass still persisted two weeks later; it did not entirely disappear until seven weeks after the onset of the disease. The child has been well since that time.

CASE 3.—A boy 6 years old was referred for operation for submental abscess in April, 1913. With the exception of scarlet fever at the age of 3 he had always been well. There are four other young children in the family; no recent illness among them. The mother knew of no children in the house suffering from mumps. The submental swelling had been present for nine days at the time I saw the patient. The illness began with vomiting and fever (102 F), pain under the tongue, and salivation. These symptoms diminished in a few hours; a median submental swelling then appeared. The patient felt well next day except for pain beneath the jaw. The submental tumor increased in size on the third day; the temperature was 100.6. The increase in size was progressive for the following two days; no change in the succeeding two days. "A little fever" has persisted, and there has been some sweating at night.

*Examination.*—Excellent general condition. Temperature, 100 F. Teeth good. Examination negative except for the local findings. The median submental swelling gives the child the appearance of having a "double chin." The overlying skin is reddened, tense, and glossy. The mass is moderately sensitive to pressure; on both sides several very small lymph-nodes are felt. The sublingual mucous membrane is bulged forward by a doughy mass underneath it; several tiny red spots, presumably the inflamed orifices of the sublingual ducts, are seen in the somewhat injected mucous membrane near the median line. By combined palpation the sublingual and submental swellings are found to

comprise a single bilocular mass. No saliva can be expressed. The other salivary glands are not enlarged. No discoverable local lesion to account for the infection.

Indifferent local applications were employed. The sublingual swelling soon disappeared, but the submental tumor remained unchanged for three days after the time I first saw the patient. It then receded gradually. Fifteen days after the onset the lesion was entirely gone. The child has remained well since that time.

These cases have been selected because they could be most closely followed and were the most striking illustrations of the affection. In some of the other patients the sublingual and submental tumefaction was not so pronounced and the peculiar persistence of the latter was not so evident. External incision of a supposed submental abscess surely would have been carried out in one case<sup>1</sup> had the affection in question not been borne in mind. In no instance was there a history of mumps among other children in the family or elsewhere in the immediate neighborhood.

At the present time the chief practical significance of the type of sublingual gland inflammation that has been presented lies in the ease with which it may be mistaken for submental abscess or other submental lesions. A brief survey of these conditions, with the question of differential diagnosis in view, may therefore be permitted.

Judging from the literature on the subject, solitary involvement of the sublingual glands in epidemics of mumps is recognizable only when an epidemic of mumps exists or when one of the characteristic complications of mumps develops. The few descriptions of "sublingual mumps" I have been able to find do not depict the pronounced local swelling, skin redness, and peculiar persistence of the lesion so frequently seen in my series of cases. An exception, on which I wish to dwell for a moment, is the unique epidemic of sublingual gland disease described in 1913 by Hegler.<sup>2</sup> He observed a group of eight cases, all adult females (seven of them nurses in one hospital), in whom the disease developed about the same time. There was no coincident epidemic of ordinary mumps. The illness began with mild febrile manifestations and a rather acute onset of the sublingual and submental swelling. The latter often reached the size of a walnut and was painful; the overlying skin was tense and glossy. The resultant appearance was frequently that of a "double chin." The floor of the mouth was swollen, the sublingual fold red and edematous in several instances. The swelling often persisted for eight to fourteen days. There were no complications. Barring the fact that Hegler's patients

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1. Transferred from the pediatric department of Dr. M. H. Bass, Mount Sinai Hospital Dispensary.

2. Hegler: Mumpsartige Erkrankungen der Zungenspeicheldruese (Sialoadenitis Sublingualis Acuta Epidemica), Beitr. z. Klin. d. Infektionskrankh., 1913, i, 229.

were all adult females, and that the disease was of epidemic nature, it is evident that his cases closely resemble those I have described.

The nonepidemic acute inflammations of the sublingual gland (and of the other salivary glands, as well) that have been described in the literature fall into two groups—one, in which the cause is purely local, the other, in which serious constitutional disease exists. Of the former, injury to the gland, diseases of the buccal mucous membrane or in the tissues about the salivary gland, calculi or other foreign bodies in the salivary ducts or gland may be mentioned. Any of the acute infectious diseases, pyogenic infections, abdominal operations or disease, cachexias, may be complicated by sialoadenitis. Lastly, the little understood salivary gland inflammation of earliest infancy should be mentioned. These varying etiologic factors play no important part in the symptomatology of acute inflammation of the sublingual glands. The condition is usually characterized by a rather stormy course: The tongue is soon elevated by the rapidly increasing swelling of the sublingual tissues, saliva flows profusely, and speech and swallowing may be difficult. The outcome is regularly the formation of an abscess that generally ruptures into the floor of the mouth or one of the salivary ducts.

This survey of the etiology and symptoms of the ordinary nonepidemic acute inflammations of the sublingual glands suffices to show that they do not resemble the type of inflammation I have described. The same statement may be made concerning the noninflammatory (?) acute sublingual lesions termed "tumor salivis" (von Bruns) and "acute ranula." In the former there is an acute transient occlusion of the salivary ducts due to definite lesions at their mouths; in the latter the tumor is cystic and is confined to the sublingual region.

Submental adenitis and frost-bite below the chin are conditions that occasionally resemble acute nonepidemic inflammation of the sublingual glands. The source of the infection in the field drained by the involved lymph-nodes will be found almost invariably in cases of submental adenitis; in the exceptional instances only a history of a focus of infection will be obtained. Separate lymph-nodes are felt in the early stages of submental adenitis; all the evidences of an abscess are present in the later stages. Sublingual swelling is manifestly no part of the picture of submental adenitis. Sublingual swelling likewise is not associated with frost-bites so often seen in the submental region. There usually is a history of exposure to cold; the lesion primarily involves the skin and the subcutaneous swelling is evidently secondary. In my experience these frost-bites never remain stationary for more than a few days; either the skin lesion recedes under appropriate treatment or, in more severe cases, sloughing and ulceration of the skin ensue.

From these remarks it is evident that the type of inflammation of the sublingual glands I have described cannot be classified at the present time with the other lesions of the sublingual glands and ducts or of the submental region. In appearance, development, and duration the clinical picture is quite distinct. On the other hand nothing in the history or physical examination points either toward or against a uniform etiology of the affection. Bacteriologic studies will be necessary to determine if there is a specific organism similar to that producing mumps, or if various etiological factors obtain. In this connection it is of interest to note that Hegler believes that a special organism, possessing a tendency to involve the sublingual glands, is the cause of the unique epidemic he described. Although his cases appeared in adult females and those I have described were nonepidemic in children of both sexes the close parallel between the clinical pictures of the two groups, to which attention has been called, cannot be overlooked in discussing their etiology.

The fact that cases similar to those I have presented are not reported in the literature appears to indicate that they are very unusual. The cases have been too frequently encountered over a period of several years to believe that this is true. From conversation with a number of physicians who see a large range of clinical material I have learned that closely parallel cases are occasionally seen. I must conclude that the significance of the described type of sublingual inflammation has been overlooked or its existence has been considered not sufficiently important to report.

#### SUMMARY

A group of cases of sublingual gland inflammation in otherwise healthy children is presented, differing in clinical picture and in etiology from the hitherto described acute nonepidemic lesions of these glands. The usual causes of acute inflammation of the sublingual glands are not in evidence.

The characteristic features are: Sudden onset of sublingual and median submental swelling with mild febrile manifestations; scattered red spots in the mucous membrane over the sublingual swelling, interpreted as inflamed orifices of the sublingual ducts; rapid increase in size, often to grotesque proportions, of the moderately painful submental swelling, frequently accompanied by pronounced reddening of the overlying skin; early recession of the sublingual swelling, contrasting with persistence of the submental tumor for one to three weeks; fever slight and general condition good throughout the course; no complications, sequelae, or recurrences.

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## A PROTECTIVE THERAPY FOR MUMPS\*

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The protection afforded to man against epidemic diseases through the employment of prophylactic antiserum injection is of course best illustrated by the case of diphtheria. It is likewise known that many infections to which animals are subject can be prevented by a similar form of passive immunization. While the number of experimental infections which can be prevented in this manner is not large, it is a notable fact that the blood of animals which have recovered from hog cholera carries a protective principle capable of warding off, for a time, infection with the filterable virus of that disease.

That human blood of one individual can be injected safely into another individual is of course a commonplace. Recent experience with the transfusion of large quantities of blood is convincing in establishing the value and safety of this procedure. Experience has also shown that human blood carrying immunity principles can be employed as therapeutic agents in several infectious diseases in man. Thus McKenzie and Martin<sup>1</sup> employed the blood serum taken from patients who had recovered from epidemic meningitis in the treatment, by intraspinal injection, of similar cases of meningitis. The blood taken from patients who have recovered from scarlet fever has also been employed,<sup>2</sup> and apparently with advantage, in the treatment of severe toxic cases of scarlet fever. Flexner and Lewis<sup>3</sup> have shown that the blood serum derived from monkeys or human beings who have recovered from epidemic poliomyelitis is capable of preventing in monkeys the paralysis which follows the intracerebral injection of the poliomyelitis virus, and Netter<sup>4</sup> has employed the serum taken from recovered human beings for the treatment of patients with acute poliomyelitis by intraspinal injection.

It is obvious, therefore, that the employment of the blood of one individual as a therapeutic agent for another is a method which in

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1. McKenzie and Martin: *Brit. Med. Jour.*, Oct. 31, 1908, p. 1341.

2. Reiss and Jungman: *Deutsch. Arch. f. klin. Med.*, 1912, cvi, Nos. 1 and 2. Reiss: *Therap. Monatsh.*, 1913, xxvii, No. 6.

3. Flexner, S., and Lewis, P. A.: *Experimental Poliomyelitis in Monkeys*, *Jour. Am. Med. Assn.*, Aug. 20, 1910, p. 662.

4. Netter, E.: *Bull. de l'Acad. d. l'Acad. d. méd.*, 1914, lxxviii, 523.

itself is without danger, and, under certain circumstances, offers advantages to the patient to be secured in no other way. Such small objections to the employment of blood as a therapeutic agent as exist can be obviated by the selection of suitable donors.

In view of these considerations it is interesting to consider what may be accomplished in preventing mumps, or epidemic parotitis, especially in institutions in which a large number of cases arise from time to time. Mumps is still to be ranked among the highly contagious infective diseases of unknown etiology, the specific causative microbic

TABLE 1.—DATA OF DONORS AND OF INJECTED PATIENTS

Donor	Age	Date of Mumps	Donee	Age	Date of Inoculation	No. c.c. Injected
1. S. C.	5½	1/30/15	H. S.	4	2/1/15	6
2. P. F.	4	1/30/15	B. K.	4	2/1/15	6
3. G. D.	4	1/31/15	S. G.	4	2/1/15	8
4. A. S.	5½	1/29/15	P. K.	3	2/1/15	6
5. I. R.	4	1/22/15	Y. G.	3½	2/1/15	6
6. J. S.	4	1/22/15	F. G.	3½	2/1/15	8
7. R.	6½	1/22/15	E. Z.	2½	2/2/15	7
8. H. H.	5	1/22/15	R. G.	2½	2/2/15	8
9. S. G.	5½	1/22/15	M. H.	4	2/2/15	6
10. G.	5	1/23/15	D. E.	3¼	2/2/15	6
11. M.	2½	1/23/15	S. S.	2¼	2/2/15	8
12. R.	4½	1/23/15	H. L.	2	2/4/15	6
13. K.	3½	1/24/15	D. G.	2	2/4/15	6
14. S.	3½	1/25/15	H. I.	3	2/4/15	6
15. M. G.	4	4/ /14	B. Z.	2¼	2/4/15	6
16. D. G.	5	4/ /14	I. S.	1½	2/4/15	8
17. L. S.	5	4/ /14	H. C.	1¾	2/4/15	6
18. B. K.	6½	3/ /13	S. G.	5½	2/4/15	6
19. J. S.	5½	12/ /12	L. S.	4½	2/4/15	8
20. L. S.	2½	12/ /12	L. S.	5½	2/4/15	6

agent not having been discovered. The disease is, however, one in which one attack yields protection that is general and persistent. The question arises, therefore, whether the blood of persons who have recovered from one attack of the disease does not contain immunizing and protective principles which can be employed in the protection of other exposed persons. Since the collection and the injection of the blood, as indicated above, are readily carried out, an effort was made this winter to control by this means an epidemic of mumps prevailing in the Hebrew Infant Asylum, which for the second time in two years was visited by a severe epidemic. The epidemic was well under way when we determined to undertake this prophylactic therapy, as may



be seen from Table 2, which shows the cases as they developed in the various wards, both previous and subsequent to the injections. At the time treatment was begun, about forty cases of mumps had broken out in the institution within the past month, and, as Table 2 shows, new cases were developing almost daily. The conditions surrounding an institution of this kind are peculiarly favorable for judging the effect of prophylactic treatment of the various infectious diseases, as most of the children are admitted during infancy, and we have complete knowledge of the infectious diseases which they have contracted while under our care.

TABLE 2.—OCCURRENCE OF MUMPS IN WARDS BEFORE AND AFTER INJECTIONS

Date	Ward No.				
	4	6	10	11	12
Jan. 22	1	6	1	1	0
Jan. 24	0	0	0	0	1
Jan. 25	1	0	0	0	0
Jan. 26	2	3	0	0	0
Jan. 28	0	0	0	0	1
Jan. 29	0	0	1	0	0
Jan. 30	2	1	0	0	1
Jan. 31	0	1	0	2	1
Feb. 8	0	1	1	1	0
Feb. 10	0	0	1	1	0
Feb. 11	1	0	0	2	4
Feb. 14	2	1	0	1	4
Feb. 15	3	0	0	0	1
Feb. 17	2	0	0	0	1
Feb. 20	3	0	0	0	0
Feb. 22	2	0	2	1	0
Feb. 23	0	0	0	1	0
Feb. 25	0	1	3	1	0
Mar. 2	0	0	0	2	2
Mar. 3	0	1	0	1	1
Mar. 4	1	0	0	0	0
Mar. 7	0	0	0	0	0
Mar. 18	0	0	0	0	0

\* Horizontal lines indicate period when injections were begun in the different wards.

Twenty children were given protective injections. They were, for the most part, children who had entered the institution before the age of one year. Naturally, none were injected who had had mumps in the course of the epidemic of the winter of 1912-13 and who had acquired immunity in this way. The ages of these children, as well as of the donors, and the amount of blood injected, may be seen in Table 1.

Whole blood was used and was injected at once intramuscularly.<sup>5</sup> The donors form three groups: The first includes children, four in number, who were just recovering from mumps; the second comprises ten children who had recovered from the disease about ten days previously; there is a third group, composed of six children who had had mumps one or two years before. It should be added that the results of the treatment in the last group cannot be considered convincing, in that three (15, 16 and 17) must be entirely left out of consideration, as they did not happen to come in contact with active cases of the disease, and because the other three (18, 19 and 20) had been in the institution

TABLE 3.—INCIDENCE OF MUMPS AMONG INJECTED AND NONINJECTED CHILDREN

Ward No.	Total Census	No. of Susceptibles	Inoculated Cases	Date Transferred to Ward	No. Cases Developing Mumps Subsequently		Remarks
					Not Inoculated	Inoculated	
4	25	22	3 (Nos. 1, 12, 14)	2/15/15	11	0	Nine cases of mumps removed from this within previous three weeks.
6	30	19	1 (No. 13)	2/11/15	8	0	Twelve cases removed.
10	30	27	1 (No. 20)	2/15/15	5	0	Four cases were removed from this ward within previous three weeks.
11	34	32	2 (Nos. 18, 19)	2/15/15	7	0	Six cases were removed within previous three weeks.
12	34	34	10 (Nos. 2, 3, 4, 5, 6, 7, 8, 9, 10, 11)	2/12/15	13	0	Ten cases were removed within previous three weeks.

but six weeks, so that we did not possess first-hand knowledge as to their susceptibility to mumps. As was to be expected from the experience of others, there were no disagreeable manifestations following the injections—neither a rise of temperature nor local reaction. The epidemic was so widespread that only three of the children under treatment did not come into contact with the disease. There are therefore seventeen who must be regarded as having been not only susceptible,

5. The blood was aspirated in the usual way and immediately injected into the patient. The procedure required so short a time that there was no need of adding any anticoagulant, and there was no disturbance due to premature clotting.

but also exposed to mumps. It is therefore striking to note that among these seventeen, none contracted the disease. That the injections were effective in bringing about this result may be seen from a glance at Table 3, which shows that in the wards where the children were not protected by injection, fully one-third, or even one-half, came down with the disease.

Our results hardly seem to require extended comment. We may add, however, that by means of these injections we were able, in a large measure, to check the epidemic. It would seem that preventive treatment of this kind could well be carried out in institutions for children, and that this simple procedure might likewise be resorted to in the home where one or more children are exposed to infection. Our experience seems to indicate that the blood may, with advantage, be obtained from the donor even before the parotid swelling has disappeared, and that it possesses protective principles at this early stage. As is well known, the incubation period of mumps is long, about eighteen days, so that it is possible to resort to protective injection some days following exposure. It is naturally impossible to state the duration of immunity acquired in this way; but it seems reasonable to believe that it well outlasts the usual danger period of infection. This type of therapy probably can be resorted to in connection with epidemics of other infectious diseases, for example, measles, in which one attack confers a marked immunity.

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# PARAPHARYNGEAL ABSCESS AS DISTINGUISHED FROM RETROPHARYNGEAL AND PERITONSILLAR ABSCESES \*

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Ordinarily a retropharyngeal abscess is easily diagnosed, an incision made from within the mouth, the pus evacuated, and an uninterrupted recovery results. In some cases, however, where there is only a retropharyngeal adenitis, no pus may be obtained by the first incision, but may be obtained later when the adenitis has broken down; or, again, the patient may recover without a second operation. In still another class of cases, incision yields little or no pus, the symptoms of fever and pain on swallowing continue, the patient becomes more septic in appearance, the tumefaction seen from within the oral cavity remains the same, while the external swelling usually increases in size. In these cases, the signs may continue unabated or may become progressively worse for weeks, even after repeated, usually unsuccessful, incisions from within the mouth, until a deep external operation is made, when, as a rule, considerable pus is evacuated and the patient recovers. It is with the view of describing, classifying, and attempting to clarify in our minds this last mentioned type of cases that this paper has been written.

*History.*—In 1903 Broca<sup>1</sup> described two cases of “peripharyngeal” abscess, with acute history, spontaneous rupture, and cure, in infants, one 6 months and one 9 months of age. He says that almost all acute “peripharyngeal” abscesses are “adenophlegmons” and involve the chain of glands along the carotid sheath, as distinguished from those in front of the prevertebral muscles.

Since then Broca, Swain and others, have written more or less extensively on this subject. Further elucidation, however, especially as regards the clinical distinctions between lateral pharyngeal abscess and conditions simulating it, and also as regards the proper method of treatment, may not be amiss. In this paper this type, i. e., the “peripharyngeal” abscess of Broca, is known, for reasons to be mentioned later, as parapharyngeal abscess.

The retropharyngeal space is limited above by the base of the skull, while below it extends behind the esophagus and is continued into the

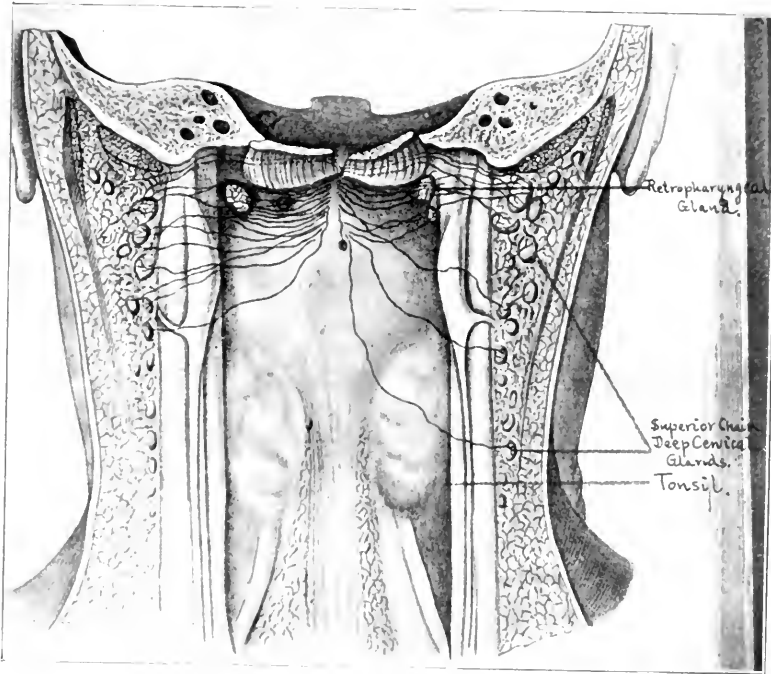
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\* Read before the American Pediatric Society at Lakewood, N. J., May 24, 1915.

1. Broca, M.: Abscès péri-pharyngiens, Bull. méd., Paris, 1903, xvii, 579.

posterior mediastinal cavity of the thorax. The lymphatics of this region, as seen by the accompanying illustration from Most,<sup>2</sup> consist of two sets of glands, viz.: (1) the retropharyngeal glands, (2) the deep cervical glands.

1. The retropharyngeal glands, small and few in number, forming a chain on each side of the median line, are found in the buccopharyngeal fascia, posterior to the pharynx and anterior to the arch of the atlas, from which they are separated by the prevertebral muscles. They receive the lymphatic drainage from the nasal cavities, the nasopharynx, and the auditory tubes. These glands atrophy in early child-



The lymphatics of the retropharyngeal space.

hood; it is extremely rare to find them after the second or third year of life. Most has never observed these glands in autopsies on older children or in adults. It is these glands from which the retropharyngeal abscesses originate.

2. The deep cervical glands, numerous and of large size, form a chain extending along the course of the internal jugular vein and the internal carotid artery, by the side of the pharynx, esophagus, and

2. Most, A.: Zur Topographie und Actiologie des retropharyngeal Drüsenabscesses, Arch. f. klin. Chir., 1900, lxi.

trachea; and extending from the tip of the mastoid to the root of the neck. They are divided into two groups, the superior and inferior. It is the superior group which interests us in this paper. This superior group drains the mouth, tonsils, palate, pharynx, tongue, posterior part of tongue, nasal fossae, interior of skull, and the deep parts of the head and neck. It is this set of glands that forms the lateral columns of the pharynx, inflammation of which causes parapharyngeal abscess, or the "adenophlegmon" of Broca.

*Etiology.*—It will be readily understood, from an anatomic point of view, how any inflammation of the rhinopharyngeal mucous membrane may be followed by a parapharyngeal, as well as a retropharyngeal abscess. Although the etiology of both conditions is practically the same, it is our observation that the retropharyngeal type is most likely to occur after the ordinary rhinopharyngitis, while the parapharyngeal type usually follows influenza, tonsillitis, scarlet fever, measles and other infectious diseases.

*Occurrence.*—Retropharyngeal abscesses occur nearly always in infancy, as the retropharyngeal nodes are supposed to atrophy after the third year of life. Most observers report the occurrence of two-thirds to three-fourths of their cases in children under 1 year of age. The so-called retropharyngeal abscess secondary to tuberculous spinal caries may occur in later childhood, even in adult life; but it is possible that the adult cases described in the literature as examples of true retropharyngeal abscess may have been cases of cellulitis or of involvement of the lateral pharyngeal glands. The parapharyngeal abscesses, involving as they do the lateral lymph chains of the pharynx, are more common after the age of 3, and probably occur more frequently than we suppose, owing to the fact that they may be mistaken for the ordinary retropharyngeal variety.

*Symptoms.*—The early symptoms of parapharyngeal abscess are those of a mild inflammation of the pharynx, occurring usually in the course of one of the infectious diseases. These may be so slight as to give no indication of the diagnosis. Then suddenly the temperature may rise to 102 or 103 F. and continue, septic in type, for several days, with no marked local signs apparent. Discomfort, difficulty in swallowing and thickness of speech usually occur. There may then appear a swelling internally just lateral to the tonsil, or externally just below the angle of the jaw and in front of the sternocleidomastoid muscle. There is seldom edema of the uvula or pharynx. The tonsil is seen to be displaced toward the median line. With this exception and the possible appearance of the internal, lateral mass, the pharynx itself may look absolutely normal. The temperature and prostration continue until the pus is evacuated externally, from which time there is, as a

rule, an uninterrupted recovery, unless the prolonged illness has exhausted the patient.

*Differential Diagnosis.*—So-called parapharyngeal abscess must be differentiated from several conditions simulating it, viz.: (1) Retropharyngeal abscess, (2) peritonsillar abscess, (3) interstitial or tonsillar abscess, (4) cervical adenitis occurring in the course of the various infectious diseases.

1. From retropharyngeal abscess. In our opinion, there is little doubt that the variety of abscesses we have styled parapharyngeal, because their site is by the side of, or lateral to the pharynx, exists as a separate entity and may be distinguished from the retropharyngeal type. The retropharyngeal abscess may produce a central bulging, though usually somewhat lateral to the midline; it does not displace the tonsil; it is as a rule accompanied by edema of the pharynx and uvula, by a brassy voice, with the symptoms of more or less laryngeal stenosis, and at times by a retraction of the head. On palpation a distinct cushionlike feeling or fluctuation may be obtained. The parapharyngeal abscess produces bulging nearer the lateral pharyngeal wall, if at all internally, but rarely in the midline; it nearly always displaces the tonsil—and this is a very important point in diagnosis—*toward* the median line, and is rarely accompanied by any marked local change in the appearance of the pharynx, or by any symptoms of pressure on the larynx. In the case of retropharyngeal abscess, internal incision usually cures, unless the suppuration extends to the lateral columns of the pharynx, at which stage the retropharyngeal becomes a parapharyngeal abscess and then requires an external incision, or burrows its way into the mediastinum. The retropharyngeal abscess is usually diagnosed early, while the parapharyngeal abscess may progress for one or two weeks before a diagnosis is made, or before the external swelling becomes sufficiently prominent to justify an external incision. Of importance also in the differential diagnosis is the age of the patient. As the retropharyngeal glands atrophy before the child is 3 years of age, an abscess in this region in a child over this age is more likely to be of the parapharyngeal form.

2. From peritonsillar abscess.

In peritonsillar abscess there is marked redness of the soft palate, and a swelling above and to the inner side of the tonsil, pushing forward the anterior pillar of the fauces. This abscess points within a few days and ruptures spontaneously or requires incision. The tonsil is not usually displaced inward as in the parapharyngeal type; the course is not a matter of weeks, as in some cases of parapharyngeal abscess and there is no external swelling.

3. From interstitial or tonsillar abscess.

These abscesses may follow a severe tonsillitis, involve the tonsils alone, rarely the contiguous tissues, and as a rule do not push the tonsil towards the midline. They cause a marked tumefaction of the tonsil itself, but never an external fluctuating mass.

4. From cervical adenitis occurring in the course of the infectious diseases.

Scarlet fever, influenza, measles, diphtheria, and tonsillitis are often complicated by acute inflammation of the superficial glands of the neck. The glands involved comprise, in practically all cases, the chain known as the superficial cervical glands, although rarely the process spreads to the deeper lymphatic structures. There is as a rule, no suppuration and consequently slight prostration; and lastly there is never any pushing inward of the tonsil—the most characteristic feature of the parapharyngeal abscess.

*Treatment.*—There is little to be said about the treatment of parapharyngeal abscess, except that repeated internal incisions so often fail to cure, that an external operation with drainage, as soon as the diagnosis is made, is, in our opinion, the ideal method. The rationale of the surgical procedure is evident, if one considers the anatomic relations of the superior chain of the deep cervical glands. The pus cannot burrow its way inward, owing to the resistance of the pharyngeal fascia, nor downward, on account of the dense capsule of the gland, and consequently it must point toward the plane of least resistance, which is externally, owing to the entrance of the glandular vessels at this site.

Brief abstracts of three cases of typical parapharyngeal abscess operated on by Dr. A. A. Berg follow:

CASE 1.—B. G., aged  $4\frac{1}{2}$  years, female. Patient had tonsillitis for several days. After this had subsided the temperature continued high, from 102 to 104 F. for two weeks. The gradual formation of an abscess was observed, which pushed the tonsil inward and produced also an external fluctuating mass. There was mild prostration, thickness of speech, and some difficulty in swallowing. There were no brassy cough, laryngeal stridor or other symptoms of retropharyngeal abscess. After an external operation the patient rapidly recovered.

CASE 2.—R. G., aged  $3\frac{1}{2}$  years, male. Three weeks after the onset of a mild scarlet fever, a swelling of the right side of the neck just below the angle of the jaw was noticed. This continued, with fever, increasing difficulty in breathing and swallowing, for one week. The tonsil and contiguous tissues were considerably swollen; the tonsil itself was displaced towards the median line. Internal incision disclosed a slight amount of pus, but afforded only temporary relief. External incision and drainage were then done, with almost immediate relief and permanent recovery.

CASE 3.—A. B., aged 3 years, male. For ten days the patient had an intermittent type of fever, ranging from 101 to 104 F., with malaise, prostration, mild cough, and rhinitis. A diagnosis of influenza was made. At the end of the first week dyspnea, dysphagia, and a swelling on the right side of the neck



were noticeable. The pharynx was only slightly reddened; there was no edema of the pharynx or uvula. There was a distinct swelling lateral to the tonsil, which appeared to displace it in the direction of the midline. The external swelling increased in size for several days, until an external incision was made, with evacuation of the pus and a subsequent gradual recovery.

#### CONCLUSIONS

1. There occurs, especially in children, a form of abscess which is occasionally mistaken for a retropharyngeal abscess, but which has a separate and distinct entity. It may be called a parapharyngeal abscess, as its site is in the lateral columns, that is, by the side, of the pharynx.

2. The origin of this abscess is from the superior chain of the deep cervical glands, which are situated along the course of the carotid artery, as distinguished from the retropharyngeal glands, situated in the circumscribed retropharyngeal space, just lateral to the midline and in front of the prevertebral muscles.

3. These abscesses are as a rule cured only by external operation.

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# PROGRESS IN PEDIATRICS

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## DYSENDOCRINISM IN CHILDREN

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### INTRODUCTION

In spite of the fact that our knowledge of the internal secretions is rudimentary and confused, great progress has been made during the last ten years in dispelling the uncertainty which surrounds their function both in health and in disease. Everyone must be convinced that these organs are second to none in the body in their influence on physiology, pathology and clinical medicine. Disturbances in the internal secretions are responsible for anomalies of growth and morphogenesis, for disturbed nutrition, disturbed excitability of the nervous system, for loss of resistance to infection and intoxications; they are also responsible for certain dyscrasias and morbid temperaments; and the equilibrium of the nervous system, especially the sympathetic, is also maintained by the internal secretions.

Johannes Müller (1844) and Ruysch showed that the blood received secretions from internal glands. The term "internal secretions" was first used in 1855 by Claude Bernard, who described the glycogenic function of the liver as the "*sécrétion interne*," while he referred to the preparation of bile as the "*sécrétion externe*."

It was Berthold of Göttingen who in 1849 first demonstrated by means of experiment, the nature of the activity of a true ductless gland: he showed the influence which can be exerted on the composition of the blood, and thus on the entire organism, by an organ through which the blood stream circulates. He removed the testicles from cocks, and grafted them on another part of the body; he found that the animals remained male in regard to the voice, reproductive instinct, fighting spirit, and growth of comb and wattles.

In 1889, Brown-Séquard, then 72 years of age, described experiments which he had carried out on himself, by the subcutaneous injection of testicular extracts. This really marked the birth of the doctrine of the internal secretions.

The first endocrinous active principle chemically isolated (in 1897) was the hormone of the adrenal medulla, which was given to the world by Abel and Crawford.

The hormone theory originated with Bayliss and Starling in 1902. They discovered that if an extract of the duodenal epithelium is injected into the blood stream a rapid flow of pancreatic juice is

determined; these observations rendered it clear that this flow of pancreatic juice must be regarded as due to the absorption of some internal secretion into the blood. To the active substance which is yielded by the epithelium cells of the duodenal mucosa they gave the name of "secretin." A similar but not identical internal secretion has been shown by Eddins to be produced by the cells of the mucous membrane of the pyloric end of the stomach. To such stimulating substances as that contained in the extract of the duodenum the term "hormone" (*ὀρμᾶω* = to stir up) was originally applied by Starling, and the expression has been extended to include the active principles of all internal secretions. Schäfer distinguishes between hormones which promote the activity of another ductless gland and those which have an inhibiting influence. To these latter he applies the term "chalones" (*χαλᾶω* = to make slack) and to the former he refers as "hormones." A chalone may therefore be defined as an endocrine product which inhibits or prevents the activity of an organ as distinguished from a hormone, which excites the tissue to increased activity; for both these substances he employs the general term "autacoid substances" (*αὐτός* = self *ἄκος* = remedy).

According to Vincent the process of internal secretion consists in the preparation and setting free of certain substances of physiologic utility (the raw materials for which are supplied by the circulating blood) by certain cells of a glandular type; the substances set free are not passed on to a free surface but into the blood stream. Organs which are not known to possess any other function than that of passing such material into the blood or lymph are termed "internally secreting" or "endocrine" organs (*ἐνδον* = within *κρίνω* = to separate). An endocrine organ may be a special organ (thyroid), a special structure of another organ (pancreas), or it may be neither special structure nor special organ, as the cells which secrete prosecretin, seem to be the ordinary cells which line the mucosa and extend into the glands.

The active materials of the internal secretions are for the most part not rendered inactive by prolonged boiling; they are dialyzable, and act readily on the cells which they influence.

The endocrine organs, although autonomous in their action, are to some extent influenced by the nervous system, and in turn their autacoids have a tremendous influence on the nervous system; many of the symptoms of dysendocrinism are due to irritation of the nervous system (especially the sympathetic) by abnormal secretions or by normal secretions in an abnormal way (hyposecretion or hypersecretion). The adrenals seem to be most influenced by the nervous system, and the gonads least. Stimulation of a certain spot in the floor of the fourth ventricle, and also at a spot in the regio subthalamica leads to increased secretion of epinephrin.

Langley divides the vegetative nervous system into two categories, the craniosacral and the sympathetic. In the autonomic nervous system he includes both the craniosacral autonomic nerves (parasympathetic system) and the sympathetic system. Many other writers, however, include only the craniosacral system in the autonomic nervous system and differentiate this system both anatomically and physiologically from the sympathetic system. The action of these two systems of nerves on the different organs which they innervate is antagonistic; for example, the sympathetic nerve accelerates the heart whereas the autonomic vagus nerve slows it.

Modern pharmacology regards as antagonists the sympathetic and the autonomic nervous system. Epinephrin is a specific stimulant of the sympathetic system by its action on the myoneural junction; pilocarpin and muscarin are specific irritants of the autonomic system. Administration of thyroid produces symptoms which simulate those of pilocarpin and muscarin, as, sweating, diarrhea, disturbances in respiration, lymphocytosis, and eosinophilia. Atropin is an antidote for pilocarpin and it also produces symptoms opposite to those of thyroid extract. It has now been attempted, on the basis of these physiologic facts, which indicate that from the thyroid gland impulses may be sent out along the tracts of the sympathetic as well as the autonomic system, to distinguish the symptoms of Graves' disease which might be due to irritation of the sympathetic, from those which might be attributed to autonomic stimulation.

#### DEVELOPMENT

It is well known that the adrenals consist of two parts, which, although anatomically united in man, are morphologically distinct and are developed from different embryonic formations. The cortex is formed from mesoderm cells of the genital ridge; the medulla is developed from cells which belong to the same neuroblast masses as give rise to the nerve cells of the sympathetic ganglia. In fishes these parts remain separate, forming "the interrenal bodies," which represent the cortex of the mammal, and the paired chromaffin bodies, which represent the medulla. In all higher vertebrates the two parts are united into one organ; it is only in mammals that the same condition is found as in man, viz., a central medulla with an enclosed cortex.

The infundibulum of the pituitary is composed of nervous tissue and expands in the interior of the gland into the pars nervosa. The anterior lobe is formed by a pouchlike outgrowth of the buccal ectoderm (Rathke's pouch). The posterior lobe is of neuro-ectodermic origin; the pineal gland, like the posterior lobe, is also of neuro-ectodermic origin.

The thyroid is found in all vertebrates; it is developed by a median outgrowth from the entoderm lining the floor of the pharynx at a level between the first and the second branchial arches. The parathyroids are developed from outgrowths of the third and the fourth visceral clefts on either side. The thymus is of entodermal origin and arises from the third branchial arch. The pancreas and the mucosa of the small intestine arise from the intestine and are therefore also of entodermal origin.

The gonads arise from the genital ridge, and are therefore, like the adrenal cortex, of mesodermal origin.

It appears that the glands which have a common origin are related in function; thus epinephrin and pituitary extract seem to have the same action; the anterior lobe of the pituitary and the thyroid, both of same origin, are related in function; and finally the adrenal cortex and the gonads, both arising from the mesoderm, are associated in the development of the secondary sex characteristics.

#### EXPERIMENTAL DATA

Total removal of the pituitary in adult dogs causes death in two or three days with symptoms of cachexia hypophysipriva. In puppies death does not follow for ten days (3-20). The symptoms of cachexia usually do not appear for from twenty-four to forty-eight hours after the removal of the gland; a marked diminution of urinary output even to anuria and a transient glycosuria may occur immediately after operation in adult dogs; and in puppies a postoperative polyuria has been observed, contrasting with the opposite condition seen in adult dogs. The symptoms of cachexia are unsteadiness of gait and lowered body temperature; an awkward arching of the back, with incurvature of the tail is characteristic; later there is still further fall of temperature, slow respiration, slow pulse, irregular muscular contractions, tremors, lethargy, anesthesia, coma and death; the temperature before death may fall 20 degrees C. Grafts in cases of total removal cause a distinct prolongation of life through this means.

The effects of posterior lobe removal are inconclusive; some of the dogs have convulsive attacks with maniacal excitement and persistent erotomania.

The results of partial removal of the anterior lobe are the same if the posterior lobe is removed also. In puppies such removal leads to infantilism. The animals remain undersized and the secondary sexual characteristics do not develop; there is also a tendency to hypotrichosis and to subnormal temperature. In adult dogs partial removal causes adiposity, sexual degeneration, subnormal temperature, hypotrichosis, polyuria and somnolence or restless playfulness.

Total removal of the anterior lobe causes death in sixty-eight hours with symptoms of cachexia; the consequences of stalk separation are equivalent to total or nearly total hypophysectomy.

They also found that repeated injections of the entire gland cause a rapid loss of weight in puppies and in adult dogs; in cases of anterior lobe insufficiency injections of anterior lobe extract cause a thermic response (from 2 to 4 C.).

The occasional appearance of glycosuria after hypophysectomy had led these observers to further study along this line. They noticed that removal of the posterior lobe and part of the anterior lobe causes a primary fall and a subsequent rise above the normal in the assimilation limit for sugars; that removal of part of the anterior lobe, however, produces little or no alteration in the carbohydrate assimilation limit; the removal of posterior lobe alone causes no primary glycosuria, unless there is considerable traumatism of the stalk, but there is an increased sugar tolerance; this increased tolerance can be brought down to normal by giving posterior lobe extract, 1/20 gm. subcutaneously, 1/80 gm. intravenously; or 2/5 gm. by mouth. In man the normal limit for glucose by mouth is 150 gm., and for levulose 100 gm. It will be seen that in case of posterior lobe insufficiency there is an increased sugar tolerance; such patients can take as much as 400 gm. of glucose without appearance of glycosuria.

To summarize, we may say that total removal of the gland, or total removal of the anterior lobe, causes death in two or three days, with symptoms of cachexia. Anterior lobe insufficiency in puppies caused adiposity, skeletal infantilism and failure in appearance of the secondary sexual characteristics; in adult dogs anterior lobe insufficiency causes adiposity and sexual degeneration. The symptoms of posterior lobe insufficiency are increased sugar tolerance, subnormal temperature, hypotrichosis, dry skin, low blood pressure, adiposity and large appetite.

#### RELATION OF DIABETES INSIPIDUS TO DYSPIUITARISM

It has long been recognized that polyuria with the appearance of dextrose in the urine is a not infrequent accompaniment of acromegaly; but it is only within the last year that both experimental and clinical evidence has accumulated to prove that diabetes insipidus is probably due to disturbed secretion of the pituitary.

In 1674 Thomas Willis first recognized a distinction between two forms of diabetes, a saccharine and a non-saccharine. Claude Bernard discovered his so-called diabetic center in 1849; this point is situated in the floor of the fourth ventricle, between the centers of the pneumogastric and the auditory nerves; puncture at a point a little lower

causes simple polyuria, while puncture at a point a little higher in the frontal direction causes albuminuria.

Cushing found that after certain experimental manipulations of the canine hypophysis, a postoperative polyuria was of frequent occurrence; in adults oliguria rather than diuresis follows a total extirpation; in younger animals there was diuresis. On the other hand, in a series of partial extirpations, postoperative polyuria was almost always observed. Experiments support the view that the clean-cut posterior lobe removals elicit polyuria with the greatest regularity. Schäfer found that posterior lobe substance given by mouth increases the urinary output; the experimental polyurias have therefore been brought about either by direct hypophysial insult, by the injection of extracts, or by glandular implantations. A hypophysial diuresis may also be elicited by nerve stimulation.

A review of the clinical histories included in many of the past articles on diabetes insipidus makes it clear that a large percentage have shown symptoms found in lesions involving the base of the brain, a gummatous meningitis affecting the structures in the middle cerebral fossa being a particularly common accompaniment of the disorder. Fuchter and Frank have emphasized the surprising frequency with which cases of primary optic atrophy, often with bitemporal hemianopsias which accompany the encephalic polyurias, are classified as diabetes insipidus. Kohler in seven of his twenty-two cases of diabetes insipidus found an affection of the infundibulum; Oppenheim in thirty-six patients with basilar luetic meningitis observed polyuria in twelve; Kruse in thirty-four cases of bitemporal hemianopsia noticed diabetes insipidus in seven cases; Oppenheim in two cases of general cerebral symptoms with double temporal hemianopsia and diabetes insipidus found on necropsy a gumma in the region of the chiasma in one case, and a gummatous meningitis in the region of the chiasma in another; in 1882 Hagenbach found a tubercle in the infundibulum of a girl ( $4\frac{1}{2}$  years old) who had suffered a good deal from thirst and polyuria; in 1903 Rosenhaupt reported a case of diabetes insipidus in which a sarcoma of the anterior lobe of the hypophysis was found; in 1913 Frank reported a case of diabetes insipidus, due to a metastatic carcinoma of the hypophysis, and Simmond reported a case due to a gunshot wound of the hypophysial neighborhood. The evidence, both experimental and clinical, is therefore in favor of the view that diabetes insipidus is probably a manifestation of dyspitu-itarism.

#### EFFECTS OF EPINEPHRECTOMY

Extirpation of both adrenals is followed by death within from twenty-four to forty-eight hours; careful removal of one adrenal is seldom fatal. If the second adrenal is extirpated some time after the

first, no effect is at first apparent; later the animal becomes less lively and exhibits signs of muscular weakness; temperature becomes lowered; weakness becomes extreme; the pulse feeble, blood pressure low, and the respiration dyspneic; death soon follows, sometimes immediately preceded by convulsions.

#### EFFECTS OF THYROIDECTOMY

Thyroidectomy produces the most marked results in young animals. There is arrest of growth, especially of the skeleton, the cartilage bones long remaining incompletely ossified. Development of the generative organs is much delayed. The integument is swollen, the surface of the skin dry, the hair thin. The muscles are limp and weak; the highest functions of the nervous system remain undeveloped.

#### EFFECTS OF PARATHYROIDECTOMY

After complete parathyroidectomy most animals die from within a few days to a few weeks; the most acute symptoms are of a nervous nature. For the first day or two there is only anorexia; later there is exaltation of reflexes, with the occurrence from time to time of fibrillar contractions of muscles, and later cramplike and clonic contractions and eventually convulsive fits; the temperature may rise 2 or 3 degrees C. during the fit; there may be attacks of rapid gasping respirations and sometimes vomiting and diarrhea; death may occur within a few days or the affection may last a long time and spontaneous recovery may take place; this symptom complex is known as "tetania parathyreopriva." The parathyroids yield to the blood a special autacoid, of a chalone nature which tends to prevent overexcitation. In animals which survive parathyroidectomy, changes in the growth and in the structure of the bones and teeth have been noted; in the teeth the calcification appears to be delayed and in the skeleton the bones generally remain smaller than in the controls; thus it is possible that these glands produce a second autacoid which is able to influence calcium metabolism; this is partly substantiated by the finding of an increased excretion of calcium in parathyroidectomized animals.

#### THYMUS

Extirpation of the thymus at the height of its development results finally in death; its most important function consists in the inhibition of acids and the consequent removal of injurious substances from the blood; it has a dominating position over the lymphatic apparatus. After thymectomy disturbances occur in calcium metabolism as well as changes in bone and in the central nervous system.



The results of thymectomy in animals which survive are:

1. The bones were generally distinctly softer and more pliable than in the control animals, and the thymectomized animals were more straddling and awkward in their gait.
2. The thymectomized animals showed less movement and less intelligence.
3. They also showed a distinct backwardness in weight.
4. Galvanic excitability of the peripheral nervous system is distinctly increased after extirpation of the thymus.

#### PANCREAS

In 1889 von Mering and Minkowski proved that the removal of the pancreas or even the greater part of the organ is immediately followed by hyperglycemia leading to a severe and fatal diabetes, whereas this effect is not obtained from mere ligature of the duct. The evidence for the action of an internal secretion which is yielded by the gland and which serves to maintain carbohydrate metabolism in a normal condition is very complete.

#### THE GONADS

It was shown by Leydig (1850) that the intertubular connective tissue is characterized by the presence of strands of epithelium-like cells; these have been termed the cells of Leydig, and collectively the interstitial gland of the testes.

If castration is performed in a child the secondary sexual organs remain undeveloped, and other male secondary sexual characters, such as growth of hair on the face and pubes, the enlargement of the larynx, and the development of the male characters of the skeleton, are arrested.

The ovary contains, besides the graafian follicles with their ova, follicular epithelium, and liquor folliculi, a highly vascular stroma formed of a peculiar connective tissue, firm in texture, and containing numerous spindle-shaped cells; these have been named the interstitial cells of the ovary and have been by some thought to be analogous to the interstitial cells of the testicle. The effects resulting from the removal of both ovaries are not so marked externally as in the similar operation in the male sex; if performed in young animals, it is not infrequently found that characters distinctive to the male are to some extent assumed; the uterus remains small; the external changes characteristic of puberty either do not occur or are greatly modified; there is no menstruation; a tendency to the male type of trichosis is often also exhibited.

Experimental evidence seems to point to the fact that the development of corpora lutea leads to the development of the mammae, the

secretion of milk, and to the hyperplasia of the uterus; its chief function seems to be related to the formation of the uterine decidua and the fixation of the embryo.

#### PINEAL

The most complete experiments yet made are those of Foà in the domestic fowl. In pullets in which the gland was destroyed no difference could be noticed on comparison with controls, but in cockerels Foà describes not only a more rapid growth of body but also an earlier development of the testicles and of the secondary sexual characters.

### *PHYSIOLOGIC ACTION OF ENDOCRINE EXTRACTS*

#### PITUITARY EXTRACT

Extracts of pituitary have a remarkable influence on the vascular system, producing a great rise of blood pressure, with contraction of vessels. The effect on the blood vessels is a direct one; the effect on the heart is different from that of epinephrin, for whereas, with the vagi cut or paralyzed epinephrin causes marked acceleration of heart, pituitary extract causes a slowing of the heart with increased force of individual beats; renal arteries are dilated and there is an increased secretion of urine. This extract powerfully affects the uterus as well as the bladder and the intestine; it also produces dilatation of the pupil of the excised eye of the frog; the secretion of the mammary gland is increased; pituitary extracts cause the disappearance of glycogen from the liver and they facilitate the production of alimentary glycosuria by lowering the limit of assimilation of sugar.

#### EPINEPHRIN

Intravenous injection causes an immediate and marked rise of blood pressure, due to contraction of peripheral arteries; concomitant with this is a slowing of the heart's action; there is some diminution in the force of respiration; the arteries of the splanchnic area are the most affected; the cutaneous vessels are strongly contracted; it is always the smaller vessels which are most affected. Other involuntary muscular tissue supplied by sympathetic fibers is also affected, as spleen, vagina, uterus, vas deferens, retractor penis; muscular contraction of intestine, stomach and esophagus is inhibited; muscles of the eye are excited so that the eye tends to protrude and the palpebral fissure appears to enlarge; the third eyelid is retracted and the pupil widely dilated; a flow of saliva is produced; the lacrimal glands are caused to secrete; as a rule there is no increase of sweat secretion.

Locally epinephrin produces marked contraction of the muscular coat.

## THYROID EXTRACTS

Intravenous injections produce (the most common effect) a marked but evanescent fall of blood pressure, dilatation of peripheral vessels and slowing of the heart. Given by mouth thyroid extract reduces blood pressure; large doses produce tachycardia, nervous excitability, flushing of skin, increase of perspiration and increase of nitrogen metabolism. If administration of thyroid is long continued the fat of the body is diminished and glycosuria may be caused; in extreme cases there may be exophthalmos and other symptoms referable to cervical sympathetic excitation, and dilatation of the pupil, psychical excitement, insomnia, tremors, and emaciation. The active substance is iodothyron or the compound protein iodothyroglobulin. The former was prepared by Baumann (1895) and found by him to contain a marked amount of iodine (0.3-0.9) per mille of dry substance.

## EXTRACT OF OTHER ENDOCRINE ORGANS

Pineal extract, like all other extracts except pituitary and chromaffin, contains depressor substances; later there is a prolonged rise, with dilatation of the kidney volume, and diuresis; there is some increase of contraction of the uterus. Pineal extract is slightly galactogogic.

Mammary extract leads to increased epinephrin in the blood; causes glycosuria, and may arrest development of the embryo, and cause abortion.

Extracts of placenta and fetus produce a chalone autacoid which have an inhibitory effect on milk secretion.

## PARATHYROID EXTRACTS

Ott found that when parathyroid extracts are given intravenously, the blood pressure is first raised, then lowered; rate of respiration is increased, diuresis is produced, and in large doses they have the effect of lowering the body temperature. Locally extracts have the power to increase the extent of contraction both in intestines and uterus and dilate the pupil.

## DYSPIUITARISM

Vesalius was the first to describe the pituitary, and in his "*De Corporis Humani Fabrica*" he named it "*glans pituitam excipiens*"; he believed that this gland secreted the nasal mucus (pituita, phlegm). Galen many years before him knew of this gland, however, and judging from its well protected location thought it was of great importance to the human economy. In 1778, Soemmering described it more fully and called it "*hypophysis cerebri*." Both Vesalius and Soemmering were of the opinion that the pituitary is a gland; but as they could not

find any duct, they considered it a part of the nervous system. Wepfer, Bonnet (1679) and Morgagni found colloid cysts in the pituitary, and Greding (1771) and Melerave observed and described enlargements of the pituitary. Wenzel claimed that diseases of the pituitary may cause epilepsy; in the light of present knowledge this is true, for many patients suffering from dyspituitarism have manifested epileptiform seizures.

In 1838 Rathke discovered the dual origin of this gland from the floor of the third ventricle and from a diverticulum of the pharynx (Rathke's pouch). In 1840, Mohr demonstrated the relation of adiposity to tumors of the hypophysis. In 1860, Liégeois, studying the anatomy of this organ, added it to the list of ductless glands. Marie and Marinesco reported two cases of acromegaly in 1886, and although they were mistaken, in that they thought this disease was due to hyposecretion of this gland, they were the first to draw attention to the relationship between this disease and changes in the hypophysis. About this time Launois described gigantism, and thought that some of these cases may be due to disease of the pituitary; but it was Cunningham who, in 1891, had proved that gigantism and acromegaly are the same disease, the only difference being that gigantism was the result of pituitary disease in cases in which the epiphyseal centers had not yet ossified, and acromegaly in cases in which ossification had taken place. In 1899 Oppenheim recognized the importance of roentgenoscopy of the sellar region as an aid in diagnosis of tumors of the pituitary. Although Pechkranz correlated adiposity with abnormal skeletal changes, with anomalies of the hypophysis, and although Babinski reported a case of tumor of the pituitary without acromegaly in 1900, Frölich is usually given the credit of describing this type of dyspituitarism, in spite of the fact that his communication did not appear until 1901. To Cushing (1909) is due the credit of putting our knowledge of the secretion of the pituitary on a scientific basis; it is he who pointed out and clearly stated the functions of the individual lobes and showed that clinically we may have many types, depending on whether one or both lobes are hyposecreting or hypersecreting. In 1912 Burnier collected a group of cases in which dwarfism is associated with hypophysial symptoms; he refers to them as cases of "hypophysial nanism."

Sir Victor Horsley was the first to publish a personal note regarding the experimental removal of the gland; the first actual contribution, however, was made by Marinesco (1892); he concluded that the loss of the whole gland was compatible with life for a long time. The first studies which include any suggestive observations on the symptomatology of a pituitarism were published in 1892, and in 1894 by

Vassale and Sacchi; among others who experimented were Cyon, Caselli, Friedmann, Maas, and von Eiselberg. The most important contribution was made in 1908 by Paulecco of Bucharest; he found that removal of the anterior lobe is equivalent to removal of the entire gland (that is, death in twenty-four hours); that loss of the posterior lobe led to no appreciable disturbances, and that separation of the stalk from the base of the brain amounted to a complete or nearly complete removal, as the case might be. In the same year (1908) appeared the notable work of Herring on the anatomy and histology of the pituitary.

The first operations on the hypophysis were by Horsley; the operative procedure in attacking the hypophysis has been studied on cadavers by Lowe and Koenig, Jr., but has been cleared essentially by Schloffer, who also operated on the first patient on the Continent in March, 1907.

#### CLINICAL MANIFESTATIONS OF DYSPIUITARISM

In man the clinical manifestations are nearly the same as those found by Cushing in dogs; the symptoms resolve themselves into those due to (1) hyposecretion or hypersecretion or perversion of the secretion of the gland itself; (2) those due to increased cerebral pressure; (3) those due to the local pressure of the tumor, and (4) those due to the involvement of the other ductless glands.

Deficiency of anterior lobe in children leads to infantilism; there is inhibition of skeletal development. Hypersecretion of the anterior lobe leads to gigantism in cases in which the epiphyseal centers had not yet ossified, and to acromegaly in adults. That gigantism and acromegaly are closely related is evident from the observations of Sternberg; he found that 20 per cent. acromegalics are over 5 feet 10 inches in height, and that 40 per cent. of all giants have some signs of acromegaly. In hyperpituitarism there is hypertrophic alteration of the skin, and increase in size of the hair follicles; there is also hypertrophy of the papillae and activation of the secretory glands, so that the skin becomes greasy and moist; hypertrichosis is marked. Deficiency of posterior lobe is usually associated with adiposity and increased sugar tolerance; the temperature is usually subnormal, and the subjective chilliness and drowsiness indicate diminished metabolism. The skin is usually smooth—may even suggest edema, but does not pit. The hair on the scalp may be abundant, but axillary and pubic hair may be entirely wanting; the nails are often small and do not show the crescent at their base. Constipation is often obstinate and usually improves on glandular therapy. Psychic disturbances are frequent and are usually due to involvement of frontal and temporal lobes. The symptoms of cerebral involvement are change in disposition, enfeeble-

ment of memory, disorientation and ". . . notable always is the utter lack of appreciation of, and complete indifference to, the existing condition." In hyperpituitarism, temperamental changes, wakefulness, lack of concentration and irritability are more common; in hypopituitarism mild psychoses to extreme mental derangements with epilepsy are not infrequent. The symptoms of increased cerebral pressure are too well known to need any detailed mention here; they are, in general, headache, general convulsions, double optic neuritis, and optic atrophy, change of position and of mental power, vomiting, vertigo, change in the pulse rate and attacks of syncope.

One of the most important local symptoms is primary optic atrophy; later there is superimposed optic neuritis due to the growth reaching a large state.

Among the most important of the local symptoms is deformation of the sella turcica; extreme hypersecretion and hyposecretion may exist with little if any alteration in the shadow cast by the bony encasement of the gland; the sella may be well preserved, even though the tumor may be enormous and has been of long duration. There are three types of sella deformation; (1) those associated with the thickening of the clinoids and dorsum sellae, (2) those with thinning from pressure absorption of these parts, and (3) those with more or less destruction of all outlines. Equally important are the abnormally small sellae, which accompany the primary glandular hypoplasias of the young.

The following symptoms present in dyspituitarism are referable to secondary involvement of the other ductless glands: imperfectly acquired secondary sexual characteristics in cases in which the lesion antedates puberty, and of resultant amenorrhea or impotence with retrogressive sexual changes, when the malady develops after the acquirement of adolescence; pigmentation of the skin, asthenia, low blood pressure and hypoglycemia point to adrenal involvement.

#### CLINICAL TYPES

One of the earliest types to be recognized is acromegaly. This type is too well known to need any detailed description. Closely associated with this type are the cases of gigantism. Both acromegaly and gigantism are due to hypersecretion of the anterior lobe; gigantism occurs in cases in which the epiphysial centers had not yet ossified, whereas, acromegaly usually occurs in adults; still cases of acromegaly have been reported in children by Antonini and Marzocchi, de Cyon, Rake, Salle and others. The most notable symptoms of acromegaly are skeletal overgrowth, main en large, phalangeal alteration, mandibular prognathism, spacing of teeth, rounding of shoulders, sterno-

clavicular enlargement, peculiar cranial configuration and hypertrichosis.

*Type Fröhlich.*—To this type belong those cases which have neighborhood symptoms of tumor of the hypophysis, without any evidences of acromegaly; these cases have a peculiar adiposity, with a feminine type of distribution of the fat when it occurs in males. There is aplasia of the genitals, hypotrichosis, subnormal temperature, undersized stature, psychoses of varying nature and increased carbohydrate tolerance. These cases are due to hyposecretion of the posterior lobe. Such cases in children have been reported by Frölich, Babinski, Hochwart, Uhlthoff, Cagnetto, Erdheim, Israel, Woolcombe, Creutzfeldt, Cushing and others.

*Type Burnier.*—In 1912 Burnier collected a group of cases from the literature and added one of his own cases, which, in addition to local signs of hypophysial tumor and signs of posterior lobe insufficiency, showed marked dwarfism. These cases are due to hyposecretion of both lobes. The most important symptoms of this type are optic nerve atrophy (almost invariably present), adiposity, dwarfism and atrophy of external and internal genitals. Such cases have been recorded by Burnier, Kon, Benda, Hutchinson, Heuter, Bartels, Nazair, Zöllner, Mixter and Quackenboss and others.

*Type Cushing.*—It is Cushing who pointed out that a pituitary may be hypersecreting at one time and hyposecreting at another, and that in fact all cases of hyperpituitarism show evidences of hypopituitarism as the disease progresses. It is he also who made the observation that one lobe may be hypersecreting and the other lobe hyposecreting at the same time; and thus we may have a variety of mixed types. He especially called attention to a case of skeletal overgrowth associated with adiposity and sexual infantilism without acromegaly.

#### DIAGNOSIS

Diagnosis of acromegaly and gigantism is simple; the Roentgen rays, however, are of great aid. They may show an enlarged sella turcica, or they may show enlargement, broadening and tufting of the phalanges. In posterior lobe insufficiency, the estimation of the sugar tolerance is of importance. We must always suspect posterior lobe insufficiency in individuals who can take more than 150 gm. glucose and 100 gm. levulose by mouth without glycosuria. In some cases of anterior lobe hyposecretion there is a thermic response when they receive an injection of anterior lobe extract. The symptom-complex of skeletal overgrowth or dwarfism, adiposity, genital atrophy, optic nerve atrophy, deformation of sella and increased carbohydrate tolerance are absolutely pathognomonic of dyspituitarism.

*DISTURBANCES OF THE ADRENALS*

The first definite account of the adrenals is given by Eustachius in 1563. In 1849 Addison observed that certain cases of disease, characterized by pigmentation of the skin, languor, and other symptoms, are associated with destruction, usually tuberculous, of the adrenal bodies. It was Trousseau who first called the condition Addison's disease. In 1894 Oliver and Schäfer discovered the blood pressure raising activity of extracts of the medullary portion of the gland. In 1901 Blum discovered that glycosuria is produced in certain animals following hypodermic injections of epinephrin. In 1897 Abel and Crawford isolated in crystalline form the active principle of the medulla of the gland. Epinephrin and iodothyroglobulin are the only definite internal secretions which have yet been isolated. The adrenal gland is built up of two entirely different tissues. Its medulla is composed of semifluid cells; these cells secrete epinephrin and when heavily loaded with this substance they take a yellow brown stain with chromate salts from which they have acquired the name of chromaffin cells. The cortex forms in man at least 90 per cent. of the entire bulk of the gland. In an encephalic fetus, the cortex is very deficient. The cortical cells seem to be concerned in supplying some secretion which influences the growth and reproductive powers of the animal; these cells are of greater vital importance than the medullary cells.

Diabetic puncture is ineffectual in animals from which the adrenals have been removed; further, in such animals the glycosuria resulting from the extirpation of the pancreas is much reduced. After prolonged use of epinephrin there is marked hypertrophy of the islets of Langerhans as well as of the adrenal bodies. As pointed out by Schäfer, there seem to be connecting links between the glycosuria set up by pancreatic removal and that due to the action of the epinephrin. After extirpation of the adrenals glycosuria cannot be produced by central puncture or by removal of pancreas. Zuelzer found that extirpation of the pancreas carried out at the same time as ligature of the adrenal veins provokes little or no glycosuria. Loewi reports that in diabetes arising after extirpation of the pancreas, epinephrin produces dilatation of the pupil if applied to the conjunctiva, whereas it has no influence on the normal eye. To summarize, it may be said that the function of the medullary portion is to sustain the cardiovascular tone and to produce an antitoxic substance capable of neutralizing toxic products of muscular activity and other undetermined poisons. There are three views as to the function of the cortex: Some believe that it has to do with the growth and development especially of the reproduc-



tive organs; others, that its main function is the neutralizing of toxic substances, and still others that it has to do with the internal secretion of the medulla. Falta believes that the cortex is a trophic center for beard growth and for the growth of hair on the body.

#### CLINICAL TYPES

##### *Hypo-Adrenia*

*Addison's Disease.*—The symptoms of this disease are too well known to need any detailed mention here. Reference to the physiologic action of epinephrin will explain many of the symptoms which occur in this disease as, hypothermia, coldness, asthenia, hypotension, emaciation, and tendency to syncope. Bronzing is due to an accumulation of melanin in the epidermal layers of the skin, and Sajous believes that the constituent of the oxidizing substance which becomes oxidized when melanin is formed is the adrenal secretion.

*Functional Hypo-Adrenia.*—Patients suffering from deficiency of adrenal secretion complain of asthenia and are very sensitive to cold; their extremities are always cold and they present the following symptoms: weak cardiac action, and pulse, anorexia, anemia, slow metabolism, constipation and psychasthenia. Children with deficient adrenal secretion are pale and emaciated; they have cold hands and feet and flabby muscles; their appetite is capricious and the blood pressure is low.

##### *Hyperadrenia*

*Tumors of Cortex.*—In hyperadrenia due to tumors of the cortex, there is an accelerated development of the body and a premature development of the genitals; the infantile type of skeleton, however, is preserved. In some cases there is adiposity; in girls there is premature onset of menstruation and development of the breasts; the hair on the mons veneris, in axilla and on the genitals develops early. Out of seventeen cases collected by Glynn fourteen were in girls. The especial feature of these cases is the early excessive development of the secondary sexual characters and the external genitals; many of these cases present adiposity; associated with the excessive and premature development of body and muscles there is premature ossification and dentition; the mental development of these patients usually corresponds with their age and not with their physical development; the sexual desires are overdeveloped but not to the same degree as are the genitals.

In older children, the symptoms of hypernephroma also manifest themselves by overdevelopment of the sexual sphere. In older girls, menstruation ceases, there is atrophy of the uterus, hypertrichosis of

masculine type (beard and mustache), hair begins to grow on the whole body, and universal adiposity develops.

It is of interest to note here that in many cases of pseudohermaphroditism of the feminine type, there is found a bilateral hypertrophy of the adrenal cortex.

The enlargement of the adrenal cortex, during breeding, during pregnancy, after castration, and the small size in deficient sexual development are additional evidence of the association of the cortex with sex characters.

#### *DISTURBANCES OF THE THYROID AND THE PARATHYROID*

In 1873 Sir William Gull gave the first account of myxedema under the name of "a cretinoid state supervening in adult life in women." Sporadic cretinism was described before this by Hilton Flagg. In 1877 Ord proposed the name myxedema. The symptoms which follow total thyroidectomy were described by J. L. Reverdin in 1882. In 1883 Kocher called this symptom complex "cachexia strumipriva." The foundations of our present method of treatment have been laid by Schiff, who had shown that successful transplantation of a thyroid gland in a dog sufficed to prevent the development of the symptoms which usually followed its removal. In 1890 Horsley suggested that grafting should be tried as a means of arresting the progress of myxedema. In 1891 Murray was first to suggest the internal administration of the gland (hypodermically); in 1892 MacKenzie and Fox showed that the extract was equally active when given by mouth.

The parathyroids were first described by Sandström in 1880. In 1891 Gley rediscovered them. The modern theory of the supreme importance of the parathyroids was first clearly put forward by Gley, and has since been elaborated by Vassale and Generali and others.

There are three directions in which the evidence of a functional relationship between the thyroid and the parathyroid glands may be regarded as conclusive:

1. There is the favorable influence of thyroid treatment in the tetania parathyreopriva of animals.
2. We have certain proof of hypertrophy of the external parathyroids, after extirpation of the thyroid gland.
3. There is hypertrophy of the thyroid which follows removal of parathyroids.

In India tetany is a disease of child-bearing women and there is a marked family tendency to the disease. The children of women who suffer from tetany are frequently cretinous. Idiopathic tetany was first described in 1830 by Stringheim.

## CLINICAL TYPES

*Hypothyroidism*

There are three well-recognized types of hypothyroidism: myxedema adultorum, sporadic cretinism, and cretinoid degeneration, which includes simple goiter, goiter heart, endemic cretinism, and endemic deafmutism. The symptoms of these various types are too well known to need repetition here. Differentiation of endemic from sporadic cretinism may be of interest, as cases of the former type may be puzzling and misleading unless one thinks of them. The effect of thyroid therapy is not so constant as in sporadic cretinism; the real myxedematous symptoms are wanting in many cases or are very slight; the manifestations of endemic cretinism are far more manifold. It is these cases which develop deafmutism, and in them are often seen great discrepancies between the physical and mental symptoms. Many of the endemic cretins show little backwardness in their mental development, although they may have all the physical characteristics of cretins, and on the other hand, some may show cretinous idiocy with but little retardation in growth. In endemic cretins growth is only delayed; even in the most severe cases union of epiphyses takes place.

Although the clinical entities mentioned in the previous paragraph are well recognized, there are many patients who present symptoms of slight thyroid insufficiency, which we are daily overlooking because the symptoms are not so well recognized.

*Symptoms of Uncomplicated Slight Thyroid Insufficiency*

The most important symptoms are (1) transitory infiltrations of the skin; (2) hirsute derangements, as partial alopecia, capillary nanism, premature baldness and grayness, absence or premature falling out of the eyebrows; (3) caloric disturbances as coldness of extremities, chilliness, shivering fits, subnormal temperature, chilliness with vasomotor derangement, of which acro-asphyxia, cyanosis, and chilblains are the manifestations; (4) anorexia, tendency to obesity and constipation; (5) fatigue and somnolence; (6) small size of patients and retardation of certain developmental processes (dentition, walking, speech); (7) tendency to muscular and articular pains and frontal and occipital headaches, as well as to apathy, indolence and depression, and (8) imperfect development of sexual glands, and diminution of sexual appetite.

Simple inadequacy of the thyroid is rarely observed clinically but is almost invariably associated with symptoms of thyroid excess. The symptoms of slight hyperthyroidism are (1) hypertrichosis and hyperthermia; (2) acro-erythrosis with cutaneous humidity; (3) emaciation and diarrhea; (4) restlessness, insomnia; (5) excessive height, developmental precocity, "syndrome of persistent juvenility"; (6) large,

brilliant protruding eyes with nystagmiform movements, extreme nervous irritability with cardiac and nervous excitability, and (7) hyperthyroidic syndromes, as migraine, ophthalmic migraine, asthma, chronic rheumatism, mucous enteritis, urticaria and certain mental symptoms.

### *Hyperthyroidism*

In 1840 Basedow described three cases of the disease which now bears his name. In 1835 Graves described the same disease, which he believed to be related to hysteria. It was Möbius who in 1886 showed the relationship of Basedow's disease to hyperthyroidism.

Holmgren had shown that Basedow's disease in children leads to accelerated growth and premature union of the epiphyses. Schkarine reported a case of the disease in a 4½ year old girl who showed abnormally rapid growth. The skeleton of such patients is gracile, and the end phalanges are pointed. In males there is impotence and a loss of libido. In women amenorrhea is an early symptom. In cases in which the disease is of long duration there may be complete atrophy of the entire genital apparatus. Conception in morbus Basedowi is rather infrequent.

Of 3,477 cases only 184 occurred in children under 15. White Clifford reported a case in an infant: the mother had one previous infant with Basedow's disease. Often a number of members of the same family have it; Oesterreich reports ten cases in one family.

It is now possible to distinguish the symptoms of Graves' disease which might be due to irritation of the sympathetic from those which might be attributed to autonomic stimulation.

#### BASEDOW SYMPTOMS

Sympathetico-Tonic	Vagotonic
1. Pronounced protrusion of the bulb.	1. Relatively moderate degree of tachycardia.
2. Von Graefe absent.	2. Pronounced subjective heart symptoms.
3. Loewi's phenomenon positive.	3. Von Graefe definite.
4. Möbius positive.	4. Wide lid clefts.
5. Dry bulbs.	5. Möbius absent.
6. Greatly increased activity of heart with less pronounced subjective disturbances.	6. Slight protrusion of the bulb.
7. Sweating and diarrhea absent.	7. Increased lacrimation.
8. Falling out of hair.	8. Profuse sweating.
9. Eosinophilia absent.	9. Diarrhea.
10. Inclination to fever.	10. Disturbances of digestion.
11. Alimentary glycosuria.	11. Eosinophilia likely.
12. Refractory behavior to pilocarpin.	12. Alimentary glycosuria absent.
	13. No epinephrin glycosuria.
	14. Pigmentation.

In 1895 von Mikulicz called attention to the occurrence of enlarged thymus in severe cases of exophthalmic goiter. In 1899 Rehn sug-

gested that it might be well to attack the thymus gland surgically in this disease. Halstead says "that the thymus plays an important part in Graves' disease has, I think, been demonstrated beyond question by the results which have followed thyroidectomy. That some sort of relation exists between the two organs we have further evidence from the physical examination of the nonfatal cases, from the autopsy table and from experiments on animals." In 40 per cent. of exophthalmic goiter cases the thymus is persistent. Symptoms of Graves' disease which indicate a preponderant influence of the thymus are the vagotonic symptoms. The blood picture in Basedow's is also due to the thymus.

#### DISTURBANCES OF PARATHYROIDS

Tetany is the most marked example of insufficient secretion of the parathyroid glands. Tetany occurs in children; it may arise idiopathically in adults, in maternity cases, in certain stomach diseases, in certain infectious diseases and under other conditions. The symptoms of tetany are too well known to need any repetition; only those which have a bearing on other ductless glands will be mentioned here.

In thyroidectomized dogs the glycosuric action of adrenin is diminished; in parathyroidectomized dogs, however, it is increased; in such animals there is also a diminished tolerance for carbohydrates. The trophic disturbances in tetany affect only tissues of ectodermal origin, as hair, nails, skin, gums, and ciliary epithelium; in chronic tetany falling out of hair is common; the nails become brittle; the skin in acute cases assumes a pseudo-edematous appearance. Often pigmentation of skin is observed. Of great interest is the development of cataract in these cases. In chronic insufficiency of parathyroid secretion there is defective development of the teeth and the bones. Some believe that such deficiency in infants leads to rickets, and in adults to osteomalacia. Other diseases which have been attributed to deficient parathyroid secretion are paralysis agitans (Landberg, 1904, Berkley, 1905), myotonia, myoclonia and myoclonic epilepsy. The coincidence of epilepsy and tetany is not infrequent. Redlich collected reports of seventy-two such cases from the literature.

*Hyperparathyroidism.*—In the few cases of adenoma of the parathyroids reported no signs of hypersecretion were noted. Lundberg and Chvostek believe that hypersecretion of the parathyroids is responsible for myasthenia paralytica. Others believe that myatonia periodica is also due to the same cause.

#### DISTURBANCES OF THE PINEAL

There are only about fifty cases reported in the literature: they are mostly due to cysts, gummata or tumors. Pineal disturbances usually affect young individuals. They are usually due to developmental defects, and are far more frequent in the male sex.

Like the hypophysial tumors, they may give the general symptoms of brain tumors with certain focal signs, and in addition, by interfering with physiologic function, may bring about distinct and characteristic disturbances in nutrition. In enlargements of the pineal, circulatory disturbances develop first, with the formation of varying degrees of hydrocephalus.

The neurologic symptoms are those of increased cerebral pressure, due to the hydrocephalus; they are always present and are among the first noted. Headache is the first symptom and is mostly occipital. Other symptoms are papillary edema, abnormal drowsiness, increased muscular tonus, weakness without paralysis of the extremities and increased reflexes. Pressure on corpora quadrigemina gives rise to ocular and papillary signs, isolated eye palsies and nystagmus. Other symptoms are giddiness and dizziness, staggering gait, asynergia and adiadochokinesis; less constantly excessive thirst, polydipsia with polyuria; glycosuria was observed in a number of cases.

The metabolic symptoms are adiposis, early sexual maturity, and later cachexia. The trophic disturbances are of most interest. There is a rapid and abnormal development of the body and premature development of the genitals. In these cases there is enlargement of the penis, with increase in genital hair and in the general hairiness of the body, increased libido, early masturbation, and in some cases changes of the voice.

Marburg believes that hypopinealism leads to premature development of the genitals, hyperpinealism to general adiposity and epinealism to cachexia.

#### *DISTURBANCES OF THE GONADS*

In the gonads (testes-ovary) there are two kinds of tissue, the interstitial tissue and the specific genital gland. The interstitial cells of Leydig in man are of the greatest importance for the development of the primary and secondary characteristics. One of the functions of the male gland may be affected without the other; for instance in abdominal cryptorchism there is no development of secondary male characteristics, but there may be spermatogenesis. In the adult, inguinal cryptorchism leads to no loss of libido. Such men may have ejaculations without spermatozoa; they are potent but sterile. They have the virile habitus; there is beard growth, skeleton is normal. Here the interstitial cells have developed but the genital cells have not. Tandler found in twenty cases of cryptorchism, spermatogenesis not once, and normal interstitial tissue in all. Ancel and Bouin tied the vasa deferentia; after a considerable time spermatogenesis ceased, but the interstitial cells were not affected. Roentgen rays affect the genital cells but not the interstitial cells.

The female and male bodies resemble each other far more before puberty than later; before puberty they both show the infantile type. In man at time of puberty the larynx enlarges, the voice changes, beard growth becomes prominent; in woman the breasts develop, the pelvis assumes the more feminine type, the form becomes more rounded, there is a deposition of fat around the hips. In both sexes there is a growth of hair on mons veneris and axillae; in woman the hair line is horizontal, whereas in man it is triangular. In man the extremities are longer in proportion to the body length.

#### HYPOGONADISM

*Eunuchism.*—If castration is carried out early, the development of the secondary sexual apparatus remains very much undeveloped (penis, prostate and seminal vesicles remain very small). In older people the penis becomes only a little smaller but the prostate diminishes considerably. There are no erections and no libido; if castration is done late, libido may remain and the subject may have ejaculations of prostatic fluid. The character of such people is entirely changed; the intelligence remains normal. Growth is accelerated and the subject may reach a height of 200 cm.; the union of the epiphyses is delayed, also ossification of sutures of head. The head is small, and the back of the head is flattened; the neck is short; the extremities are long and lower part from umbilicus is longer than above. The pelvis remains infantile; the voice and the larynx remain childish. The bones remain delicate and the muscular markings are fine; the skin is thin and pale and of yellow discoloration. There is adiposity of feminine type, a horizontal fold of fat at the mons veneris, and a deposit of fat on the nates, on the hips, thighs, mammae. The secondary male characteristics are poorly developed. The hair on the head is well developed, no beard growth, no hair on body, in axilla, or on scrotum and perineum.

Castration after puberty in women leads regularly to atrophy of the uterus and vagina; menstruation ceases, the clitoris shrinks and libido diminishes; in a few cases there was increased libido for a time; adiposity generally present.

*Eunuchoidism in Adults.*—Here we get all the symptoms of eunuchs except the bone changes, as the epiphyses have already united. The penis, testicles, and prostate all become small and atrophy; there is no libido; impotence is present; there is a retrogression of all the male secondary sexual characteristics. In women there is a retrogression of the genitals and adiposity and a loss of pigment, but no loss of hair in axilla or from mons.

## HYPERGONADISM

Hypergonadism has been noted in children suffering from malignant disease of ovary or testicle. In these cases there is enormous development of the body; the hair on the mons, in the axilla, and on the face begins to grow; hair grows also over the whole body. Libido is developed as in adults. Intelligence is well developed but childish; premature change of voice takes place. Erections and ejaculations have been noted as early as in the first year; in these cases the hyperdevelopment of the genitals precedes the development of the body. There is premature closure of the epiphyses, so that these children are too big for their age, but they cannot become giants; the body shows infantile dimensions.

In females, there is *menstruatio praecox*; the uterus, vulva and breasts are overdeveloped. There is excessive bodily growth; dentition, changes of teeth, ossification of bone centers, and closure of epiphyses are premature. One of these children was impregnated at 8 years; shortly after this the abnormal growth ceased; she died at the age of 75 years (von Haller).

*DISTURBANCES OF THE THYMUS*

Neusser reported a case of tumor of the thymus in a man aged 25 years; the patient was very tall and hypoplasia of the genitals was present. In many cases of myasthenia gravis, hyperplasia of the thymus is found. After operative removal of the gland, even in infancy, hardly any symptoms are observed. But in most of these cases only partial removal was performed so that no definite conclusions can be drawn. Thymus hyperplasia is very often found in Basedow's disease, in acromegaly and in eunuchs.

Katz, in each of sixty-one mentally normal children who died of various diseases, found a normal thymus; in each of twenty-eight mentally feeble children, the thymus was absent. In another series of 292 cases of mentally deficient children the organ was absent in 74 per cent. Lange, Decker, Garri, and Lampè have reported cases of idiocy in which at necropsy the thyroid was found quite normal; the thymus was very small.

Ruhräh and Thompson found atrophy of the thymus in marasmus cases. Thymectomy causes a gradual decrease in the leukocyte count, while an administration of thymus causes an increase of these cells.

In status thymolymphaticus, there may be increased height, gigantism, or dwarfism; the bones may present deformities as in osteitis deformans or acromegaly. The head may be larger or smaller than normal and may present other anomalies; the extremities are long; the epiphyses close late. The facies is pasty and anemic. Adiposity of a



eunuch type is usually present; the development of male secondary characteristics is deficient; the male form approximates the female configuration. Hair supply is deficient on body, and scrotum; no beard growth; voice is high pitched; pomumadami only slightly developed; penis, testicles and prostate all small; cryptorchism and aspermatogenesis are often present. This description given by Neusser corresponds very clearly with our present conception of hypogonadism; and as in most of Neusser's cases there was concomitant cryptorchism and aspermatogenesis it is very likely that the symptom complex which he ascribes to status thymolympathicus may be due to hypogonadism.

In women Neusser noted a deficient hair growth; menstruation delayed or entirely absent; uterus hypoplastic; pelvis small; infantilism of internal genital organs; manly voice; masculine build of larynx and distribution of hair; flat breasts, small hips, hypoplastic heart; congenital mitral stenosis and other congenital heart anomalies, especially congenital narrowing of the aorta and other blood vessels.

#### *DISTURBANCES OF THE PANCREAS*

Bouchardt observed sclerotic changes in the pancreas in cases of diabetes. Mering and Minkowski proved that total extirpation of the pancreas in dogs leads to glycosuria. The opinion was expressed by Laguesse (1893) that the so-called islets of Langerhans may be the seat of the internal secretion of the pancreas. Opie and Weichselbaum proved that in diabetes mellitus the islets are the seat of pathologic lesions.

In the glycosuric stage of diabetes, injections of epinephrin increase the output of sugar, but in the aglycosuric stage no such increase is noted. After thyroidectomy, however, epinephrin glycosuria is diminished, but after parathyroidectomy it is increased.

Claude Bernard could produce glycosuria by puncturing a spot in the fourth ventricle. This glycosuria is produced through the sympathetic system; if the spinal cord above the outlet of the sympathetic is broken no such glycosuria results. Electric stimulation of the splanchnic produces glycosuria. Glycosuria is also found in cerebral hemorrhages, encephalomalacia, tumors of the brain, and especially in tumors of the fourth ventricle.

Hyperglycemia is also produced in extirpation of pancreas, in Bernard's puncture, or puncture of the medulla, stimulation of the splanchnics, and by the introduction of an excess of epinephrin into the blood. An increased sugar tolerance is observed in hypothyroidism, in hypopituitarism and in hypo-adrenalism. In hypogonadism, although there is adiposity, the tolerance for carbohydrates is limited and alimentary glycosuria is more easily evoked.

In many cases of diabetes there is increased excitability of certain sympathetic nerves, especially of the dilator of the pupil, of the liver, kidney and other organs; but the excitability of the autonomic nerves is not diminished.

In diabetes, impotence is usually found in men, but there is no recession of the secondary sex characteristics. Often there is atrophy of the testicles. In women menstruation is not disturbed but conception is rare. Bramwell and Reutone have described cases of pancreatic infantilism in children.

#### CLINICAL MANIFESTATIONS OF PLURIGLANDULAR DISTURBANCES

To the axiom that a man is as old as his arteries may be added that a child is as old as its ductless glands. The ductless glands, like other organs, may prematurely degenerate; at times this is due to inherited insufficiency of the glands, to infection, or to intoxications; the result is a sclerotic atrophy of a number of these glands. Most affected are the thyroid gonads, hypophysis and adrenals. In addition to symptoms of deficient secretion of these glands a terminal cachexia usually develops.

All these cases show symptoms of late hypogonadism. Cachexia and anemia are prominent symptoms; no adiposity occurs, but emaciation with weakness is nearly always present. The face and other parts of body are swollen as in myxedema. Alopecia and loss of hair on the whole body usually take place; pigmentation of skin and mucous membranes is a prominent symptom. Anemia and transient polyuria are at times present. In women degeneration and atrophy of the genital apparatus and of the secondary sexual characteristics is very marked.

In these cases, degeneration of the genitals and retrogression of secondary characteristics is referable to hypogonadism. Alopecia, trophic disturbances of the nails, and teeth, the apathy, headaches and amnesia and myxedematous skin are due to hypothyroidism. The cachexia and the transient polyuria suggest the involvement of the hypophysis. The hypotonia, the severe asthenia and the pigmentation point to the involvement of the adrenals. Spasmophilia and tetanic contractions suggest that the parathyroids may also be involved.

Thompson in a case of marasmus found marked sclerosis of all the ductless glands. Hutchinson, Gilford and Variot and Pironeau\* have reported cases of pluriglandular involvement in children. Variot named these cases *nanisme type sénile*. The cases reported by these

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\* Since the article was written another case of progeria was reported by C. W. Rand, Boston Med. and Surg. Jour., 1914.

writers resemble each other as do all cases of cretinism. There is retardation of growth in these cases (may be dwarfed); emaciation with folding of the skin is a prominent symptom. The muscular development is good, but the skeleton remains infantile; the bones are delicate, ends are thickened and the epiphyses close prematurely. The genital development is much retarded; there is deficient hair growth over the whole body, including head and eyebrows, which imparts to these patients a very senile appearance. On necropsy in one of these cases only sclerosis of the pituitary was found. Intelligence in these cases was good. Gilford has named this condition "progeria."

#### *"INTERRELATION OF THE DUCTLESS GLANDS"*

Although our knowledge of the internal secretions is incomplete and confused, much progress has been made in this branch of medical science in the last decade. One fact has been clearly brought out and that is that the physiologic relation of all ductless glands is an intimate one, and that in pathologic conditions of one of them all the other glands are affected. The influence of one gland on another may be compensatory or inhibitory.

The existence of a relationship between the thyroid and the hypophysis is perhaps the most satisfactorily demonstrated of all the possible interrelations of endosecretory organs. The pituitary hypertrophies as a reaction of hypothyroidism. The thyroid exercises normally an inhibition on the pituitary, but stimulates the adrenals; the adrenals inhibit the pancreas, and the pancreas inhibits both the thyroid and the adrenals; the adrenals, however, stimulate the thyroids. In Basedow's disease we have menstrual disorders, amenorrhea, and often atrophy of sex organs; in myxedema we have sex depression, impotence and atrophy of the genitalia. There exists some relationship between these organs, and it is probable that the thyroids have on the sex organs a stimulating effect that is necessary for the normal continuance of their function. In Basedow's disease and in simple congenital goiter, the thymus is often enlarged. In Switzerland the offspring of goitrous mothers often have both thymus and thyroids enlarged. Thyroidectomy raises the assimilation limit for dextrose; therefore the thyroid inhibits the pancreas in its function of promoting glycolysis.

The pituitary has a slightly stimulating effect on the thyroid. These glands are more or less synergic and either can to some extent function vicariously for the other. Cushing found atrophy of the gonads after extirpation of part of the anterior lobe. In acromegaly there is cessation of menstruation, impotence in the male, and atrophy of aplasia of the genitals. The pituitary, therefore, supplies a secre-

tion that stimulates the sex glands to activity. After prolonged feeding of pituitary there is hyperplasia of the adrenal cortex.

A theory that the adrenals are related to the sex functions was proposed by Meckel as early as 1906. It was based on the following grounds: 1. In certain aborted fetuses he had noticed that both the adrenals and the gonads were lacking. 2. In animals in which sexuality is marked the adrenals are notably large. 3. In birds and amphibia the gonads and the adrenals are closely associated in position. 4. He had

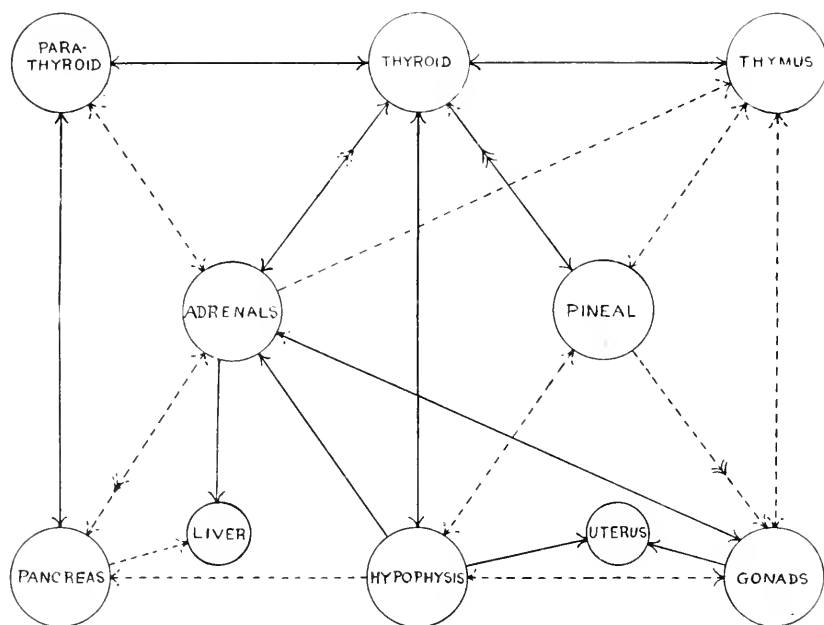


Fig. 1.—Chart showing interrelation of endocrine organs. ———→ stimulates; ———→ inhibits; <——> cooperate; <——> antagonize; A <——> B <——> C; A and C cooperate « »; A stimulates B——>; B inhibits A <——; B inhibits C ———>; C has no action on A.

noted adrenal degeneration in several cases of disease of the genitalia. In cases of hermaphroditism marked hypertrophy of the adrenals is sometimes observed. The clinical literature indicates that there is a correlation between the adrenals and the gonads. It further suggests that the adrenals furnish a stimulus to the gonads. In Addison's disease there is hypertrophy of the thymus. The adrenals and the pancreas are mutually antagonistic. In Addison's disease the dextrose limit is high.

Castration causes hypertrophy of the anterior lobe of the pituitary; pregnancy also causes increased activity of the hypophysis. The pituitary is normally held in check by the gonads and when this inhibi-

tion is removed the pituitary manifests increased activity. The gonads exert a depressing effect on the thymus; the adrenal cortex hypertrophies after castration: the thyroid hypertrophies in menstruation and in pregnancy (Fig. 1).

#### INFANTILISM

The term "infantilism," devised by Laségne, means the maintenance of the genital organs in the infantile state of development, with a lack of secondary sex characteristics; there is a failure of the primary and the secondary sex characteristics to appear at the proper time. This may occur in individuals of dwarf growth, of normal growth, and in giants.

Infantilism occurs: (1) in the dwarfing of growth from intoxications as chronic tuberculosis, congenital lues, malaria cachexia, leprosy, pellagra, in severe rickets, chronic alcoholism in childhood, after prolonged and excessive doses of mercury, lead, morphin, tobacco and carbon bisulphid; (2) in all abnormalities of growth which seem to depend on the gross lesions or defects of important internal organs as thyroid, pituitary, gonads, thymus, pancreas, adrenals, kidney, and liver (in fact all dwarfs except achondroplasiacs present infantilism and puerile habitus); (3) in disturbances of growth associated with disturbances of the circulatory system either congenital or beginning very early in life, congenital stenosis of the aorta, stenosis of mitral and aortic valves of the heart, and general defects of the circulatory system; (4) in conditions such as congenital adiposis, progressive muscular dystrophies, microcephaly, spastic diplegia, and ateliosis.

The Brissaud type of infantilism manifests itself mainly by the persistence of the characteristics of childhood, physical and mental, without the evidences of true idiocy and often without true dwarfism. This type of infantilism is probably due to hypothyroidism, and presents the symptoms of myxedema in a mild form.

#### "DWARFISM"

Dwarf races seem to have been mentioned in the literature and legends of most languages. Schweinfurth found at the court of King Munza representatives of a dwarfed race to whom he applied the name "Akka." There is among the proletariat of European cities and elsewhere, a great group of very undersized individuals; these are said to be especially common in Bavaria and Italy. Among famous dwarfs may be mentioned Æsop, Philetas of Cos, Alypius, Licinius Calvus, Characus, and Carrie Akers, height 2 feet 10 inches, weight 309 pounds.

Growth depends on inherited disposition, nutrition, conditions of life, as surroundings or environment, and habits of life; pathologic

influences may affect any of these. Dwarfs may be classified into (1) cases which may be possibly caused by either changes of condition or by inherited tendency or both; (2) cases occurring in one or more children, as the defective growth which occurs in lues, in children of drunkards, or those affected by plumbism or other poisons; and also cases of ateliosis or true dwarfism; (3) cases in which influences to growth are brought to bear during intra-uterine life, for instance, dwarf growth of microcephaly or porencephaly; (4) cases in which adverse influences have been exerted during childhood; here, development, at first normal, has after an illness ceased to advance at the usual rate, for instance, in acquired hydrocephalus, chronic meningitis, malaria, cachexia, granular kidney, pneumonitis, congenital heart disease, early acquired heart disease, chronic alcoholism in early childhood; (5) cases due to disorders of the pituitary, thyroid, thymus, adrenals, pancreas and intestine (Herter); (6) cases occurring in connection with rickets, ateliosis, and achondroplasia.

Dwarf growth may be the result of insufficient development, the premature ossification, and the early union of the epiphyses and diaphysis (achondroplasia). Or it may be due, as in true dwarfs (ateliosis) to a persistence of the cartilage disks throughout life. In these cases epiphyses do not join the diaphyses; in many bones the epiphyses do not appear at all, being represented by cartilage as in the infant; there is no disproportion in the trunk and the extremities. In cretins the cartilage of conjugation persists, ununited with the diaphysis. Eruption of teeth is disturbed in all dwarfs except achondroplasiacs; persistence of milk dentition and delayed eruption of last molars, are common in true dwarfs, in cretins and in microcephalics.

Achondroplasiacs enter the world as such; in true dwarfs the stunting of growth may be congenital or acquired soon after birth or during infancy, or childhood; in these, growth may be retarded to a minimum, or it may be very slowly continuous until quite late in life (thirtieth year). In others growth, having ceased, may recur and slowly continue until still later in life. Few of these reach old age, but many have lived 100, 90, 80, or 75 years.

Ateliosis resembles cretinism in facial appearance and in the same peculiar configuration of the skull. Defective development of the genital organs and the puerile habitus are other features common to both. In the true dwarf the deficiency of intelligence occasionally goes as far as idiocy. These two groups seem to merge into one another. And if ateliosis is to be considered a manifestation of dysthyroidism, then achondroplasia must also so be considered, for these two conditions present diametrically opposed symptoms. Myxedema in association with achondroplasia has been recorded more than

once; sporadic cretinism and achondroplasia may occur in different children of the same family. Dr. Hergothe has also alluded to the existence in the same family of achondroplasia and obesity, rickets and myxedema. Cavazanni records a case of achondroplasia in a child whose mother was afflicted with Graves' disease, and Duranti one of similar association, in which the mother died of liver and renal disease.

The differential points between ateliosis and achondroplasia will be noted from the following:

#### ACHONDROPLASIA

Height: Smallness of height, 3 feet 6 inches; 4 feet, 3 feet 2 inches.

Head: Large, round, brachycephalic; frontal and parietal eminences prominent; face small but with large features.

Muscular Development: Excessive; arms are muscular, very short; tips do not touch beyond the great trochanters.

Limbs: The lower limbs are short and massive; show angular deformities above and below the knees. Midpoint may be a quarter of the total height above the symphysis; shortening of limbs is of rhizomelic type. Hands and feet are short, thick, broad fingers of equal length. Main *en trident*.

Nose: Is flat and broad, retroussé nostrils are large.

Genitals, intelligence, hair, trunk, larynx, skin, dentition normal.

#### ATELIOSIS

Height: At 9 years, 19½ inches; at adult age 32½ inches.

Head: Face and general appearance those of infancy; face is short and broad; head proportionally large, is high, quadrate, prominent eminences; lower jaw and chin are small; head is brachycephalic.

Muscular Development: The musculature proportionate to size; is weak and shows lincaments of childhood.

Limbs: Hands, feet and nails have shape and appearance of childhood; no deformation; the skeleton shows the ridges, grooves and points of musculative origin and insertion; are feebly marked; physical strength is small, though greater than that of children of the same height.

Nose: Bridge depressed; broad; saddle shaped; is short and undeveloped.

Genitals: Secondary sex characteristics wanting; are usually sterile; incomplete descent of testes is usual. There is usually but not always sexual infantilism.

Intelligence: Usually normal; may vary from slightly defective to idiocy.

Hair: No hair on face; neck is short and thick; on the head not abnormal.

Trunk: General bodily proportions are those of normal child; mid part a little above the upper border of symphysis; the proportionate length of the segments of the limbs to one another is also normal.

Larynx: Is small and undeveloped; voice high pitched.

Skin: Not thickened, though it shows wrinkling and bronzing.

Dentition: Delayed.

The Lorain type or dwarfism was described by Lorain (1820). The dwarfism is symmetrical; it nearly always affects males. There are no myxedematous symptoms present, and the genitalia are usually normal; the pubic and axillary hair is wanting. The stature is diminished and slender; the facial appearance, expression, and intelligence are normal. This is not due to hypothyroidism but to anangioplasia,

that is, a defective development of the arterial system, and to premature ossification. This condition is probably due to an underlying status lymphaticus.

#### *GIGANTISM*

Bollinger includes under giants only those who have attained a height of 205 cm. Brissand and Meige believe that acromegaly and gigantism are one and the same disease; that acromegaly is gigantism in a person in whom the epiphysis had not yet united. Sternberg found that 40 per cent. of all giants have manifestations of acromegaly, and that 20 per cent. of all acromegalics are giants. Gigantism is not infrequently met with in eunuchs and in cases of hypogonadism. Huchard and Launois reported a case in a son of a giant; this boy was of gigantic stature at 12 years; at 18 he was 197 cm.; the genitals were normally developed; he lived to 60 years and then developed typical acromegalic manifestations. In the early stages of acromegaly, there is increased sexual potency and libido at times, but usually there is impotence, whereas "the interstitial cells of Leydig" are not affected; or there is hyperfunction of these cells; but in giants without acromegalic symptoms, there are manifestations of deficient secretion of the Leydig cells from the beginning.

#### *ADIPOSITY*

Von Noorden divides adiposity into two classes; one depends on exogenous and the other on endogenous factors. Exogenous adiposity is due to overeating, which often leads to diabetes; the endogenous adiposity is due to disease of ductless glands. Von Noorden showed that glycogen fixation and sugar production may be disturbed, while the fat formation from carbohydrates, may still continue. The fat tissue absorbs the overproduced carbohydrates as fat; there is thus an actual diabetic metabolism disturbance, but without glycosuria; thus we may have a pancreatic adiposity.

Hypothyroidism leads to adiposity; hunger cures in these cases lead to weak heart, but thyroid administration causes great reduction of fat; other signs of hypothyroidism are present. There is much increased tolerance for carbohydrates.

In dystrophia adiposo-genitalis, the fat is distributed in a peculiar way. This really is not an adiposity, for if these patients become emaciated they still preserve the fat pads in their choice places. But at times there is general adiposity in hypophysial cases and then it is due to increased sugar tolerance. These cases do not respond to thyroid, but often do respond to pituitary or testicular extract. The adiposity of pineal disease is probably due to hypophysial involvement.

In adipositas dolorosa, there is a peculiar distribution of the fat; the fat masses are painful, later asthenia and psychical symptoms



develop. Dercum believes it to be a type of dysthyroidism. In eleven cases which came to necropsy, nine showed changes in the thyroid. Of seven cases in which the hypophysis was examined, five showed pathologic changes.

#### THE BLOOD

In all diseases of the thyroid, hypophysis, and adrenals there is a diminution of neutrophils and an increase of the mononuclears, especially the lymphocytes; in half the cases there is leukopenia and in many cases there is eosinophilia. One often finds the same blood picture in status thymolymphaticus, and it is possible that the blood picture in dysendocrinism may be due to an underlying condition of status lymphaticus.

#### SUMMARY

In hypogonadism in children, there is increased height; the skeleton is gracile and shows characteristic dimensions (from sole to umbilicus longer than above, wide span and small head). There is characteristic fat deposition and deficient development of secondary sex characteristics. The closure of epiphyses is delayed, as is the ossification of bone centers.

In hypothyroidism there is dwarfism or retardation of growth; the skeleton retains the infantile type; the closure of the epiphyses is much delayed; ossification of bone centers is retarded and the fontanels close late. The ossified bones show slight sclerosis; the bones are plump (in young people with Basedow's disease, there is slight acceleration of growth and premature closure of union). There is retardation of genital development but not to the same extent as in hypogonadism.

Hypopituitarism in children leads to retarded growth; closure of epiphyses and ossification of bone centers is delayed. There is hypoplasia of the genitals, and especially marked non-development of secondary sex characteristics; adiposity of hypogonadism type and skeletal dimensions also resemble those seen in hypogonadism. In young acromegalics, there is premature closure of epiphyses, marked accentuation of secondary characteristics, and premature thickening of the bones with exostoses. In other cases there is retarded development of the genitals with gigantism of type seen in hypogonadism.

In hypergonadism, hyperadrenalism and hyperpinealism, there is premature development of the whole body, accelerated growth with preservation of infantile dimensions, premature development of the genitals, and later, premature closure of the epiphyses; these children are too big for their age, but they can never become giants on account of the closure of the epiphyses.

The closure of the epiphyses and therefore the extent of growth seem to be under the influence of the gonads. The development of

centers of ossification and the length of the bones seem to be greatly influenced by the thyroid and the hypophysis. In growth retardation due to the thyroid the bones are plump, in that due to the hypophysis they are delicate. In children, however, in Basedow's disease the bones are delicate, and in young acromegalics, they are plump with exostoses.

The anterior lobe of the pituitary and the thyroid control growth; hypersecretion leads to increased growth or gigantism, diminished secretion to diminished growth or dwarfism. Hyposecretion of thymus and pancreas may also lead to diminished growth.

Hyposecretion of the posterior lobe of the pituitary causes adiposity; hypersecretion causes glycosuria and polyuria.

The secondary male sexual characteristics are controlled by the interstitial cells of Leydig and are greatly influenced by the adrenals. The adrenals seem particularly to be related to the growth of a hair on the face and body.

The genital organs are controlled by the interstitial cells, but are secondarily affected by the pituitary, the thyroid, the adrenals, the pineal and the thymus.

Adiposity is present in hyposecretion of posterior lobe of the pituitary, in hypopinealism, in hypogonadism, and in hypothyroidism. It is usually associated with increased tolerance for carbohydrates, except in hypogonadism, in which there is no such increased tolerance. Tendency to glycosuria is present in hypersecretion of posterior lobe of pituitary, in hyperthyroidism, and in hyperadrenalism. Hypothermia is usually associated with adiposity, and hyperthermia with cases in which there is a tendency to glycosuria.

Carbohydrate metabolism is primarily regulated by the pancreas and the adrenals; the pancreas regulates glycogen formation, and the adrenals glycogen fixation; protein metabolism seems to be controlled by the thyroid; the purin bodies by the hypophysis, and the thyroid and calcium excretion seems to be controlled by the parathyroids and the thymus. The hypophysis, the thyroid, and the parathyroids also influence carbohydrate metabolism by their secondary influence on the adrenals and the pancreas. For analysis of the other symptoms see chart.

#### *ILLUSTRATIVE CASES\**

CASE 1.†—Hypopituitarism of both lobes with Basedow's disease (Fig. 2). A. K., 12 years of age. The patient had been complaining of headache, double vision, vertigo and vomiting; he was always cold and suffered a good deal from constipation. Weight 93 pounds, height 53 inches (12 pounds overweight, 4

\* Cases 2 to 8, inclusive, are from the Pediatric Department of Vanderbilt Clinic, service of Dr. C. H. Smith.

† Case 1 has been previously reported in connection with an article on Dyspituitarism, *AM. JOUR. DIS. CHILD.*, September, 1913.

TABLE OF VARIOUS CONDITIONS DUE TO DISTURBANCE OF DUCTLESS GLANDS

[illegible]

inches under height). Facies was peculiar and expression anxious; slight exophthalmos was present. Adiposity was of a feminine type of distribution; the genitals were hypoplastic and there was no axillary and no pubic hair. The pulse was 84 to the minute; the temperature subnormal. Bitemporal hemianopsia was present; mentality normal. The sella was enlarged and the centers of ossification were normal; the carbohydrate tolerance was increased to 250 gm. The presence of genital hypoplasia, hypotrichosis, adiposis, skeletal under-



Fig. 2

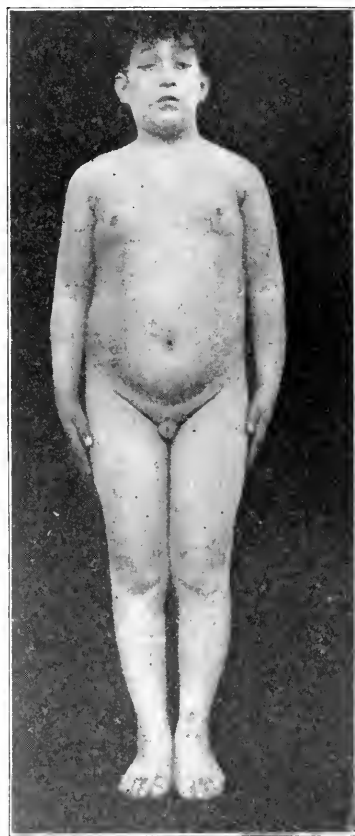


Fig. 3

Fig. 2.—Boy of 12, showing hypopituitarism of both lobes with Basedow's disease (Case 1).

Fig. 3.—Boy of 12 with functional hyposecretion of anterior and posterior lobes of the pituitary (Case 2).

growth with symptoms of cerebral pressure and enlarged sella suggest a tumor of the hypophysis; the presence of exophthalmos tachycardia and tremor suggests the presence of hyperthyroidism which is probably of a compensatory nature.

CASE 2.—Functional hyposecretion of anterior and posterior lobes of the pituitary (Fig. 3). F. P., aged 12, was brought for the rapid development of adiposity, which is of a feminine type of distribution. The temperature is subnormal. He complained of drowsiness and headache. Eye fundi were normal. Height is 4 feet 7½ inches; weight 111 pounds. The sella showed slight enlargement; the ossification centers were normal; the carbohydrate tolerance was increased. The adiposity, the hypoplasia of the genitals, the hypotrichosis, the hypothermia and the increased carbohydrate tolerance suggest posterior lobe insufficiency. Absence of cerebral symptoms rules out neoplasm.



Fig. 4



Fig. 5

Fig. 4.—Boy of 5 with hyposecretion of anterior lobe and hypersecretion of posterior lobe of the pituitary; diabetes insipidus (Case 3).

Fig. 5.—Child of 17 months with hypopinealism (Case 4).

CASE 3.—Hyposecretion of anterior lobe and hypersecretion of posterior lobe of the pituitary; diabetes insipidus (Fig. 4). O. F., aged 5 years. The patient had been passing a large quantity of urine (120-140 ounces per day) for the last two years; the thirst was very marked. Weight was 32 pounds, height 37 inches; temperature always about 100 F. Genitals were hypoplastic and the testes undescended. The urine showed a specific gravity of 1.007, no albumin, and had a trace of sugar. Roentgen ray of sella showed a very small pituitary; ossification of wrist centers was delayed; the hands were like those of a cretin. The mentality was normal. The polyuria and the glycosuria suggest hypersecre-



Fig. 6



Fig. 7



Fig. 8



Fig. 9

Fig. 6.—Child, aged 28 months, with hypothyroidism (Case 5).

Fig. 7.—J. A., achondroplasiae, aged 6 years.

Fig. 8.—A. A., aged 12. Precocious maturity.

Fig. 9.—Case of ateliosis, aged 23. Height 25 inches; weight 12 pounds.

tion of the posterior lobe; the skeletal undergrowth may possibly be due to hyposecretion of the anterior lobe.

CASE 4.—Hypopinealism. A. B., aged 17 months (Fig. 5). This case presents the following symptoms: adiposity, abnormal development of the breasts, and premature ossification of the head and bone centers of the wrists; circumference of the head only 17 inches; mentality far above that of usual infant of its age; marked spasticity of the legs and exaggerated reflexes. The fundi and the sella are normal. The precocious mental development, the adiposity, the premature ossification and the presence of cerebral symptoms with a normal sella suggest the presence of hypopinealism.

CASE 5.—Hypothyroidism (Fig. 6). I. S., aged 28 months; typical facies and hands of mild cretinism; marked physical and mental backwardness; genitals hypoplastic; temperature subnormal; ossification of bone centers of wrist much delayed; marked improvement under thyroid treatment.

CASE 6.—Achondroplasia (Fig. 7). J. A., aged 6 years.

	November, 1911	November, 1912	November, 1914
Head .....	20 inches	20 inches	20½ inches
Chest .....	18 inches	19½ inches	20 inches
Abdomen ....	20 inches	23 inches	20 inches
Length .....	29 inches	31½ inches	34½ inches
Weight .....	26 pounds	28 pounds	34 pounds
Navel-sole ...	13¾ inches	14½ inches	18 inches

CASE 7.—Precocious maturity? Hyperadrenalism? A. A., aged 12 years (Fig. 8), sister of child whose case is reported above. Began to menstruate at 10 years; she had been sent to a sanatorium for pulmonary tuberculosis. She shows abnormal development of the breasts and of the pubic and axillary hair. This is a case of precocious maturity or it may be a case of hyperadrenalism due to tuberculous involvement of the adrenals. The mentality was normal for the age.

CASE 8.—Ateliosis (Fig. 9).—The female (Fig. 9) is 23 years of age and is 25 inches in height; the weight is 12 pounds. Mentality is normal for the age. She presents no deformities; she is a true dwarf.

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## THE PROTEIN NEED OF INFANTS

BEING METABOLISM STUDIES OF A TWO MONTHS' OLD INFANT FED WITH  
VARYING PROPORTIONS OF COW'S MILK PROTEIN \*

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DETROIT

The problem of determining the optimum quantity of protein necessary for the growing organism has been the subject of numerous observations. The result of feeding to an infant large quantities of protein over a prolonged period has not been studied to the extent it deserves and it was with a desire of increasing our knowledge on this subject that the work detailed in this paper was carried out.

It has been shown many times that the growing organism requires a certain quantity of protein for the replacement of tissues due to "wear and tear" as well as for growth of body, true growth being intimately associated with the retention and fixing of nitrogen compounds as integral parts of the body. No doubt the amount of protein required varies from time to time in accordance with what Mendel<sup>1</sup> has been pleased to call the "growth impulse." However variable may be the demands of this "growth impulse" for protein, it can never be as variable as the supply which is furnished, particularly in artificially fed children. When the baby is breast fed the protein intake is more constant, although it naturally will vary with the protein content of the milk, being highest in the first few days of lactation, quickly diminishing as colostrum changes to milk, and then remaining fairly constant to the end of lactation. Barring these variations the breast fed infant is subjected to much less disturbance in protein supply than the average artificially fed child.

The proportion of protein supplied in mother's milk should be a helpful criterion in determining the protein requirement. In his

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\* Read at a meeting of the American Pediatric Society held at Lakewood, N. J., May 24, 25 and 26, 1915.

1. Mendel: Trans. Fifteenth Internat. Cong. on Hyg. and Demog., Washington, 1913. ii. 429.

Harvey Society Lecture Howland<sup>2</sup> has stated this point clearly. He says:

There is every reason to believe that the amount [of protein] furnished a healthy nursing infant represents at least a sufficient quantity and cannot be much in excess. However, since only 80 per cent. of the nitrogen of human milk is available (the other 20 per cent. being in the form of urea and extractives) one may, when feeding cow's milk, where practically all the nitrogen is available, reduce the quantity of protein to an amount equal to 80 per cent. of that supplied by mother's milk. Since about 8 per cent. of the total energy of mother's milk is supplied by protein, and since 20 per cent. of this energy is in a form which cannot be used, one may from this line of argument decide that 6.4 per cent. of the total energy of a food should be in the form of utilizable protein.

This argument is quite contrary to modern practice. Rubner<sup>3</sup> however brought out this point clearly some time before when he suggested that the diet of the growing infant should be relatively poor in protein. He based his finding on the results obtained in studying the nitrogen metabolism, which showed that a child kept up normal growth when 7 per cent. of its total energy intake was in protein; that 5 per cent. was sufficient for maintenance; that even 4 per cent. was sufficient to supply its actual need when amply supplied with carbohydrate.

Rubner's original discussion is appended in footnote 3.

Whether a child be fed naturally or artificially, therefore, it is evident that protein up to a maximum of 7 per cent. of its caloric need will meet all its requirements.

In the course of its existence the child increases in musculature and activity; its "wear and tear" quota increases and the "growth impulse" impels the organism to increase its bulk of protoplasm, and thus there is generated an active demand for protein. Should this demand be not supplied, then, according to Rubner<sup>4</sup> the "growth impulse" becomes latent, there is no growth, even "wear and tear" is not taken care of. Again, should this demand be just supplied, then growth takes place and tissue is renewed. But what results when protein is supplied in excess? Can it stimulate growth? In reply to this Rubner<sup>5</sup> ten years ago said: "Growth is not proportional to the quantity of the protein in the diet." "Protein cannot raise the rapidity of growth above the limits set by nature."

2. Howland: Harvey Society Lecture, March 29, 1913.

3. Rubner: Im Hinblick auf diese Verhältnisse ist es schon in hohem Masse interessant, dass in der Wachstumkost die von Heubner und mir beobachteten Säuglinge überhaupt nur 7 per cent. in Kalorien in Eiweiss geboten waren, und dass bei Erhaltungskost sogar nur 5 per cent. des Kalorienumsatzes auf Eiweiss treffen, ja wenn man die Resorptionsverhältnisse noch mit heran zieht, so reichte der Säugling vollkommen für seine Bedürfnisse mit einem Umsatz, von dem nur 4 per cent. auf das Eiweiss treffen, Arch. f. Hyg., 1908, lxvi, 97.

4. Rubner: Arch. f. Hyg., 1908, lxvi, 109.

5. Rubner: Arch. f. Hyg., 1908, lxvi, 110.

What, then, becomes of the additional protein fed, over and above the need for maintenance and growth? To quote Rubner<sup>5</sup> again, "As the amount of the protein in the diet increases, a smaller percentage is utilized [for growth] and the excess of the intake is merely consumed in place of an equivalent of non-nitrogenous food."

The question then naturally arises, can any harm come to a growing organism through the feeding of an excess of protein?

To answer with any degree of thoroughness one must inquire as to the various changes which protein undergoes in its transition from an external food product to the cell of the living organism.

Before being absorbed into the body all protein must be first split into amino-acids, as has been so clearly demonstrated by Abderhalden.<sup>6</sup> These amino-acids when once within the body combine and are built into the tissues, forming new cells or repairing old ones. But what becomes of those amino-acids absorbed in excess of the need for repair and growth?

Rubner,<sup>7</sup> discussing this point, believes that the excess is eventually oxidized in the same manner as carbohydrate and fat. His original language is appended in footnote 7.

There is a further question, viz., Just what is the effect on the growing organism of the combustion due to the metabolism of the protein? A number of observations have been made which show in part the results which follow an increased ingestion of protein for short periods.

Howland<sup>8</sup> working in Prof. Lusk's laboratory was able to demonstrate an increase in the heat production of 10 per cent. by addition of 15 gm. (5 gm. to each of three feedings) of nutrose, a dried casein product containing 89.06 per cent. protein, to the food of a child 3 months of age, and an increase of 26 per cent., by addition of 30 gm. nutrose per day to the diet of another child 7 months of age.

Table 1, based on Howland's<sup>9</sup> work, shows the effect of excess protein on the carbon dioxide as well as the heat output in Child 1 (3 months old) and Child 2 (7 months old).

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6. Abderhalden, E.: *Synthese der Zellbausteine in Pflanze und Tier*, Berlin, 1912, p. 101.

7. Rubner: Das Eiweiss, welches über den bedarf des ersatzes (E) unter das wachsthum (W) hinaus aufgenommen wird, vertritt dann die sonst verbrauchten Nahrungstoffe, Fett oder Kohlehydrate, ist also im gewissen Sinne eine überflüssige Zufuhr und zudem unter Umständen durch die dynamischen Wirkungen ein an sich entbehrlicher Energieverbrauch, *Ztschr. f. exper. u. Therap.*, 1905, i, 1.

8. Howland: *Ztschr. f. physiol. Chem.*, 1911, lxxiv, 1.

9. Howland: *Trans. Fifteenth Internat. Cong. on Hyg. and Demog.*, Washington, 1913, ii, 430.

Murlin and P<sup>10</sup> showed an increase of 12.5 per cent. in the metabolism of a 2 months'-old baby when the proportion of the calories in the food arising from protein was raised from 11 per cent. to 29.6 per cent. Details of the experiment when tabulated are as shown in Table 2.

Before discussing the results of the work covered by this paper I wish to express my thanks to Prof. Lusk, of the Physiological Department of Cornell University Medical College, and Dr. L. E. LaFétra, Chief of the Children's Service in Bellevue Hospital, for many helpful

TABLE 1.—EFFECT OF EXCESS PROTEIN ON CARBON DIOXID AND HEAT OUTPUT IN INFANTS

	Length of Time Studied	Food	CO <sub>2</sub> Per Sq. Meter Per Hr.	Calories Per Square Meter Per Day	Increase Per Cent.
Child 1....	Average of eleven sleeping hours	One-half milk and sugar	17.01	1,094	..
Child 1....	Average of four sleeping hours	Same and 15 gm. nutrose	18.21	1,210	10
Child 2....	Average of seven sleeping hours	Three-fifths milk and 5 per cent. sugar, and 30 gm. malt extract	19.21	1,270	..
Child 2....	Average of five sleeping hours	Same plus 30 gm. nutrose	23.64	1,595	26

TABLE 2.—INCREASED METABOLISM IN AN INFANT FROM INCREASED PROTEIN

	Length of Time Studied	Food	Calories Per Hour	Calories Per Sq. Meter Per 24 Hours	Increase Per Cent.
Child C. P., aged 2 months	Average of four sleeping periods	Dil. cow's milk, 11 per cent. protein cal.	7.32	907.5	....
Child C. P., aged 2 months	Average of two sleeping periods	Ei weissmilk, 29.6 per cent. protein cal.	8.12	1,021	12.5

suggestions and constant encouragement. Thanks are also due to the corps of efficient assistants who very kindly cooperated in the technical operation of the calorimeter. According to a plan outlined by Prof. Lusk it was decided to begin with a low protein diet and determine metabolism on such a diet for this child and then gradually to increase the protein content relatively and actually, maintaining the fat and carbohydrate content as nearly as possible on a level throughout the observations.

10. Murlin and Hoobler: AM. JOUR. DIS. CHILD., 1915, ix, 81.



The child was under observation sixteen days in all, being in the calorimeter two or more hours daily from March 24 to April 10, inclusive, except the two intervening Sundays, March 28 and April 4, during which time thirty-seven periods of one hour each were studied, the first six periods being studied in the respiration chamber devised by Dr. Murlin,<sup>11</sup> in which the metabolism was determined by indirect method and the balance in the small calorimeter of the Atwater-Rosa type in which the metabolism was determined both directly and indirectly. The work of the Murlin apparatus demonstrated its efficiency, since the findings under same conditions of food, repose, time after feeding, etc., were practically identical with those obtained with the Atwater-Rosa calorimeter.

Throughout these entire sixteen days the child was kept on the metabolism frame devised and described by me<sup>12</sup> and seemed in every way as comfortable as in the hospital crib. Without a single exception the urine was completely and accurately collected and daily analysis was made of its nitrogen content.

The caloric value of all food given was determined by bomb calorimetry, and the nitrogen content of each day's feedings was carefully determined by the Kjeldahl method, so that there was a perfect record of the caloric as well as of the protein intake. Incidentally this revealed some startling discrepancies between the supposed and the real value of milk formulas as usually made up, and indicated the very great necessity of actually determining the caloric value of food by bomb calorimetry in all metabolism studies in which the caloric intake is considered. The bomb calorimeter used was that devised by Mr. Riche, under whose guidance the work was done.

The infant chosen for this series of observations was a robust, healthy boy aged 2 months, who had been deserted by his mother after having been brought to the hospital. He had been under observation in the hospital for some time and was gaining in weight, taking his feedings well and the stools were perfectly normal.

The first four days the child was fed on one-third whole milk with 5 per cent. dextrimaltose added, during which time the metabolism on low protein diet was determined. The child was then placed for one day on slightly increased protein diet, and the following day was put back again on low protein diet; this continued each alternate day, gradually increasing the protein intake, until the last five days, when the child was placed on maximum quantities of protein in the form of albumin milk prepared by the Walker-Gordon Laboratory. The protein on certain of these days was increased by the addition of nutrose, and on the last day double strength albumin milk was fed.

11. Murlin: *AM. JOUR. DIS. CHILD.*, 1915, ix, 43.

12. Hoobler: *AM. JOUR. DIS. CHILD.*, 1912, iii, 253.

The clinical condition of the child continued normal up to the last two days of the series, when it was noticed that the child no longer took an interest in his surroundings, and gradually entered into a state of semistupor. The pulse was slower and there were times when the respirations were slightly irregular. The stupor continued for a few days after the observations ceased. The child on being taken off the metabolism bed was put back on the same diet on which he was before the studies began. The stupor gradually lessened, so that within one week the child was normal again and began to gain in weight.

During the first eleven days the weight gradually increased, but there was a rapid loss during the last five days. The quantity of urine diminished greatly but no acetone bodies were present and the

TABLE 3.—ENERGY METABOLISM WHEN FED ON COW’S—

Date, 1914	Period No.*	Weight in Gm.	Surface Area per Sq. Meter $y=mx+b$ (Howland)	Kind of Food	Distribution of Cal. in Food	Cal. per Kilo.	Cal. in Last Feed-ing	Cal. in 24 Hrs.
3/24	1	4,364	0.2830	Diluted cow's milk with sugar added	P.11%-F.25%-CH.64%	80	39	351
3/25	1	4,371	0.2840	Diluted cow's milk with sugar added	P.12%-F.27%-CH.61%	74	36	324
3/26	1	4,350	0.2830	Diluted cow's milk with sugar added	P.12%-F.27%-CH.61%	74	36	324
3/27	2	4,350	0.2830	Diluted cow's milk with sugar added	P.14%-F.27%-CH.60%	74	36	320
4/ 1	1	4,406	0.2858	Diluted cow's milk with sugar added	P.12%-F.27%-CH.61%	77	42	338
Av. of 5 sleep-ing periods	.....	.....	.....	.....	P.12.2%-F.26.4%-CH.61.4%	76	33	331.4

\* Sleeping periods only used.

stools became yellow and watery. The temperature was taken both in the calorimeter and in the ward and at no time was it found to be above normal, but on the contrary was slightly below normal at times.

The deleterious results of feeding large amounts of protein has already been hinted at under the term “*Eiweissnährschaden*” by Salge,<sup>13</sup> but he was unable to give the specific clinical symptoms accompanying such injury, and so far as I am aware the clinical symptoms above described have never before been charged to an excess of protein in the diet. The condition was not one of so-called acidosis, for it was not accompanied by the dyspnea typical of that state, neither was the carbondioxid output lowered. The urine did not contain the acetone bodies. The appearance also differed from acidosis in that the child lay in a motionless position with eyes wide open and staring. The features were not drawn. There was no difficulty in breathing, but rather there was a slowing of respiration. As soon as the protein

13. Salge: *Kinderheilkunde*, Berlin, 1912, p. 112.

was diminished the symptoms gradually disappeared and child became normal. It seems to me that symptoms similar to the above but less pronounced may be observed in various stages of malnutrition when children are fed on sugar and fat-poor diet.

Passing now to a study of the tables presenting the work done, we note that Table 3 gives in detail the various data incident to the metabolism studies when the child was fed on a low protein diet. Attention should be called to the remarkable similarity of results obtained from day to day when the child was studied under like conditions of food, repose, time, etc. The average of the five days establishes a metabolism on low protein of 893 calories per square meter of body surface per twenty-four hours.

—MILK (DILUTED) AND SUGAR, BEING A LOW PROTEIN DIET

Time Since Last Feeding	Respiratory Period	CO <sub>2</sub> per Hr., Gm.	CO <sub>2</sub> per Sq. Meter per Hr., Gm.	O <sub>2</sub> per Hr., Gm.	R. Q.	N in Urine in 24 Hrs., Gm.	N in Feces in 24 Hrs., Gm.	Cal. Produced per Hr., (Calcu- lated)	Cal. Pro- duced per 24 Hrs.	Cal. per Sq. Meter per 24 Hrs. (Howland's Formula)
1 hr. 45 min.	10:45-11:45	3.91	13.8	3.07	0.92	0.924	.3450	10.56	259.5	895
1 hr. 38 min.	10:38-11:38	3.96	13.9	3.19	0.92	1.008	.4060	10.74	256.7	907
2 hrs. 10 min.	11:10-12:10	4.00	14.1	3.20	0.93	1.008	.4060	10.75	259.2	912
1 hr. 54 min.	11:54-12:54	4.13	15.5	3.25	0.92	1.008	.5953	11.31	256.8	907
36 min. ....	10:36-11:36	4.07	14.2	3.00	0.99	1.169	.2819	10.54	241.6	845
.....	.....	4.01	14.1	....	....	.....	.....	10.78	254.8	893

The standard agrees very closely with that obtained for children under 3 months as published by Murlin and me.<sup>21</sup>

Table 4 gives detailed data of the sleeping hours obtained when the child was fed on a high protein diet. There were ten of these periods and the table shows the results obtained in each period as well as the average of all these periods.

It will be noted that the calories per hour gradually increased as the proportion of protein was increased, and that the average per hour for the ten sleeping hours was 12.74, and that the calories per square meter per twenty-four hours were 1,120.

Table 5 is a comparative table of the averages of the hours on low protein with those on high protein.

It will be noted that the twenty-four hours' caloric intake averaged about the same; that the proportion of protein calories in the food was raised from an average of 12.2 per cent. to 40.2 per cent. and that the resultant metabolism shows an increase of 25.4 per cent.

This confirms the work of Howland and establishes the fact that the protein of cow's milk when fed in excess of need increases the metabolism.

It is important here to discuss the effect on the infant of this increase in heat production.

Generally speaking, it has heretofore been assumed that the heat regulating mechanism of the body could take care of this additional heat without detriment to the growing organism. The only word of caution which has been spoken has been based on the fear that during summer days when the weather is warm this additional heat could not

TABLE 4—SHOWING ENERGY METABOLISM—

Obs. Day and No.	Period No.*	Weight of Gm.	Surface Area per Sq. Meter $y=mx+b$ (Howland)	Kind of Food	Distribution of Cal. in Food	Cal. per Kilo.	Cal. in Last Feed-ing	Cal. in Food in 24 Hrs.
2	1	4,390	0.2850	Albumin milk from whole milk plus dextrimaltose	P.16.7%-F.25.6%-CH.57.7%	121	56.0	448.1
6	1	4,406	0.2858	Albumin milk, cream, dextrimaltose, maltose	P.15.1%-F.24.7%-CH.60.2%	74.5	43.6	327.3
8	1	4,406	0.2858	Albumin milk, cream, dextrimaltose plus 5 gm. nutrose	P.21.0%-F.23.8%-CH.55.2%	68.0	55.1	297.7
10	1	4,320	0.2768	Albumin milk with 15 gm. nutrose added	P.43.7%-F.29.3%-CH.27.0%	73.5	38.8	310.7
10	2	4,320	0.2768	Albumin milk with 15 gm. nutrose added	P.43.7%-F.29.3%-CH.27.0%	73.5	38.8	310.7
10	3	4,320	0.2768	Albumin milk with 15 gm. nutrose added	P.43.7%-F.29.3%-CH.27.0%	73.5	38.8	310.7
13	1	3,761	0.2546	Double strength albumin milk from fat-free milk. No sugar added	P.56.2%-F. 0.0%-CH.43.8%	80.0	37.6	300.8
13	2	3,761	0.2546	Double strength albumin milk from fat-free milk. No sugar added	P.56.2%-F. 0.0%-CH.43.8%	80.0	37.6	300.8
13	3	3,761	0.2546	Double strength albumin milk from fat-free milk. No sugar added	P.56.2%-F. 0.0%-CH.43.8%	80.0	37.6	300.8
12	3	4,220	0.2768	Albumin milk with 28 gm. nutrose added	P.50.1%-F.25.0%-CH.24.9%	84.0	50.4	353.9
Av. of 10 sleeping periods					P.40.2%-F.18.7%-CH.41.1%	80.8	43.4	326.2

\* Sleeping periods only used.

escape. The heat regulating mechanism in the adult may well be adapted to dissipate this increased heat production, but infants whose heat regulating functions are still partially undeveloped are unable to avail themselves of the many means which the adult uses to get rid of extra heat, such as change of environment or adding to or lessening amount of clothing worn; and the habit of over-dressing babies for fear of "catching cold" tends to increase the difficulty of dissipating the heat due to this increased metabolism.

The cause of this increased metabolism was at one time attributed to the production of "free heat" when protein was oxidized in the

body, but the latest researches of Prof. Lusk<sup>14</sup> show that "amino-acids even when they are not oxidized yield products of metabolism which act as stimuli to induce higher oxidation in that organism. This is a conclusive proof of a true chemical stimulation of protoplasm within the mammalian organism. It explains the specific dynamic action of protein."

Turning our attention to a study of protein retention with the view of determining whether this increased heat is due to protein ingested, protein oxidized, or protein added to the body, Table 6 shows the quantity of protein ingested, oxidized and added to the body, on each

—WHEN FED ON HIGH PROTEIN FOOD

Time Since Last Feeding	Respiratory Period	CO <sub>2</sub> per Hr., Gm.	CO <sub>2</sub> per Sq. Meter per Hr., Gm.	O <sub>2</sub> per Hr., Gm.	R. Q.	N in Urine in 24 Hrs., Gm.	N in Feces in 24 Hrs., Gm.	Cal. per Hr., (Calculated)	Cal. Produced in 24 Hrs.	Cal. per Sq. Meter per 24 Hrs.
32 min. ....	10:32-11:32	4.15	14.6	3.19	0.95	1.183	.2846	11.08	260.35	943
30 min. ....	10:30-11:30	4.14	14.5	3.48	0.86	1.113	.1876	11.95	283.43	992
30 min. ....	10:30-11:30	4.16	14.5	3.04	0.99	1.155	.2309	10.77	253.89	888
38 min. ....	10:38-11:38	4.04	14.6	2.97	0.99	2.367	.5182	10.46	243.92	881
1 hr. 38 min.	11:38-12:38	4.36	15.7	4.03	0.79	2.367	.5182	13.45	320.23	1,156
2 hrs. 38 min.	12:38- 1:38	4.77	17.2	4.60	0.75	2.367	.5182	15.35	362.93	1,311
44 min. ....	10:44-11:44	3.92	15.4	3.65	0.78	2.403	.6457	12.22	300.5	1,178
1 hr. 44 min.	11:44-12:44	4.31	16.9	3.82	0.82	2.403	.6457	12.28	306.0	1,205
2 hrs. 44 min.	12:44- 1:44	4.21	16.5	4.44	0.68?	2.403	.6457	14.71	347.8	1,366
2 hrs. 36 min.	12:36- 1:36	4.50	16.2	4.63	0.71	2.347	.6766	15.13	362.9	1,311
.....	.....	4.256	15.61	....	....	.....	.....	12.74	304.20	1,120

of the days when low protein was given and Table 7 shows the same data for days of high protein ingestion. Table 8 shows the averages compared, indicating an average increase of 49.4 calories on high protein, an increase in metabolism of 20 per cent.

Table 9 shows an increase in an individual period much above the average, this result having been obtained on the day the highest quantity of protein was fed, with an increase in the metabolism of 108 calories or 42.5 per cent., which is the greatest increase yet recorded.

In Table 10 it will be noted that in each of the two periods the same amount of heat was produced and practically the same amount

14. Lusk: Jour. Biol. Chem., 1915, xx, 815.

TABLE 5.—COMPARISON OF ENERGY METABOLISM AS OBTAINED ON DILUTED COW'S MILK  
AND WHEN FED ON HIGH PROTEIN MILK MIXTURES

	Food	Degree of Repose	Distribution of Calories	Cal. in 24 Hrs.	CO <sub>2</sub> per Hr., Gm.	CO <sub>2</sub> per Sq. Meter per Hr., Gm.	Cal. Pro- duced per Hr. (Calcu- lated)	Cal. Pro- duced per Sq. Meter per 24 Hrs.	In- crease Per Cent.
5 Hrs.	Low protein diet	Sleeping	P.12.2%-F.26.4%- CH.61.4%	331.4	4.01	14.1	10.78	893	
10 Hrs.	High protein diet	Sleeping	P.40.2%-F.18.7%- CH.41.1%	326.2	4.25	15.6	12.74	1,120	25.4

TABLE 6.—PROTEIN BALANCE SHEET

Date	Type Diet	Protein in Grams			Total Calories Produced
		Fed	Oxidized	Added to Body	
3/24 .....	Low protein	9.42	6.975	2.445	259.5
3/25 .....	Low protein	9.48	6.870	2.610	256.7
3/26 .....	Low protein	9.48	6.870	2.610	256.7
3/27 .....	Low protein	11.18	9.170	2.010	256.7
4/ 1 .....	Low protein	10.05	8.287	1.763	241.6
Average 5 hours.....	Low protein	9.90	7.630	2.27	254.8

TABLE 7.—PROTEIN BALANCE SHEET

Observa- tion Day No.	Period Number	Type Diet	Protein in Grams			Total Calories Produced
			Fed	Oxidized	Added to Body	
6	1.....	High protein	12.5	8.13	4.37	283.4
8	1.....	High protein	14.7	8.66	6.04	253.9
2	1.....	High protein	18.2	9.17	9.03	200.3
10	1.....	High protein	33.1	19.03	15.07	243.9
10	2.....	High protein	33.1	18.03	15.07	320.2
10	3.....	High protein	33.1	18.03	15.07	362.9
13	1.....	High protein	41.3	19.05	22.25	300.5
13	2.....	High protein	41.3	19.05	22.25	306.0
13	3.....	High protein	41.3	19.05	22.25	347.8
12	3.....	High protein	43.3	18.90	24.40	362.9
Average 10 hours.....		High protein	21.1	15.6	15.5	304.2

of protein was oxidized. There were also different quantities of protein ingested as well as vastly different quantities of protein added to the body. In each of these periods there was an increase of metabolism of 42.5 per cent. over the heat produced on "low protein" as already shown in Table 9. If this increase in heat production were

TABLE 8.—PROTEIN BALANCE SHEET

Length of Observation	Type Diet	Protein in Grams			Total Calories Produced	Increase in Metabolism*	
		Fed	Oxidized	Added to Body		Calories	Per Cent.
Av. 5 hours...	Low protein	9.90	7.630	2.27	254.8		
Av. 10 hours...	High protein	31.1	15.6	15.5	304.2	49.4	20.0

\* The per cent. of increase is here figured on the absolute increase regardless of weight or surface area, hence is lower than when figured on basis of square meter of surface.

TABLE 9.—PROTEIN BALANCE SHEET

	Type Diet	Protein in Grams*			Total Calories Produced	Increase in Metabolism	
		Fed	Oxidized	Added to Body		Calories	Per Cent.
Av. 5 hours...	Low protein	9.90	7.630	2.27	254.8		
12th day .....	High protein	43.3	18.90	24.40	362.9	108.1	42.4

\* Only the third hour is used in computing, as the first and second hour child was restless. This is the highest increase in metabolism due to protein yet recorded.

TABLE 10.—PROTEIN BALANCE SHEET

No. of Observation	Type Diet	Protein in Grams*			Total Calories Produced	Increase in Metabolism	
		Fed	Oxidized	Added to Body		Calories	Protein
10 .....	High protein third period	33.1	18.03	15.07	362.9		
12 .....	High protein third period	43.3	18.9	24.4	362.9		

\* These figures show that the increase in metabolism arises from protein oxidized rather than protein added to body. It will be noted that "Protein Oxidized" and "Calories Produced" are the same, while amount "Added to Body" is much increased.

dependent either on the amount of protein ingested or on the quantity of protein added to the body, then the two periods would have differed in heat produced, but the heat produced being the same in each it is evident that the quantity of protein oxidized is the determining factor in the increased heat production. Therefore it follows that the metabolism of protein necessary for growth or for replacement of "wear and

tear" of tissue are not factors in producing this additional heat, but the increase is due to the protein oxidized as shown in Table 10. Since, according to Rubner, all protein not necessary for growth and repair is oxidized, one might conceive that such excess of protein because of its stimulating effect on metabolism might become a positive detriment to the organism. Frequently by reason of the increased metabolism more heat was given off than was supplied in the intake of energy, thus causing the organism to draw on its stored-up supply of energy, as shown in Tables 11, 12 and 13.

Table 11 shows the proportions of the various foodstuffs ingested and metabolized when fed on low protein food. It will be noted particularly that 77.3 per cent. of the protein intake was oxidized and that 86.7 per cent. of the fat and carbohydrate intake was metabolized.

Table 12 shows the same information when the child was fed on high protein.

Table 13 shows a comparison of the averages of the two preceding tables and reveals one of the most interesting facts of this paper. It will be noted that the daily caloric intake on the two diets was about the same, viz., 331 and 326 calories; that the proportion from protein was so much increased that it reduced the caloric intake from fat and carbohydrate, viz., 198.2, considerably below what was being regularly metabolized under low protein feeding, viz., 225. The amount of calories, however, derived from the metabolism of fat and carbohydrate under high protein feeding remained practically the same, viz., 234, as under low protein feeding. In other words, there were 198 calories fed and 234 oxidized. Where, then, did these other 36 calories come from? Undoubtedly from body glycogen and fat.

This shows particularly well in Table 12 on the thirteenth day when there were but 131.5 calories in the food derived from fat and carbohydrate, and yet there were 233.5 calories produced from the oxidation of fat and carbohydrate in the body, or 102 calories more than fed. It seems clear from this that when protein is ingested in high proportions with fat and carbohydrate in relative low proportions, the metabolism process required a certain minimum to be supplied by fat and carbohydrate, and when not supplied, the calories required over and above those ingested must be drawn from the stored up fat and glycogen. In other words, protein food when given in excess, stimulates the infant's metabolism to such an extent that the energy liberated from the increased protein metabolism may be insufficient to furnish this increase in the heat production of the organism. Howland's work showed similar results.



TABLE 11.—FOODSTUFFS INGESTED AND METABOLIZED ON LOW PROTEIN DIET

Child Fed on Low Protein Diet		Total Food Calories				Protein				Fat and Carbohydrate			
Day	Period	Intake	Me- tabo- lized	Per Cent. of Intake	In Food		Metabolized		Per Cent. of Total Food Intake	In Food		Metabolized	
					Calo- ries	Gm.	Calo- ries	Gm.		Calo- ries	Gm.	Per Cent. of Intake & CH.	Per Cent. Derived From Fat CH.
3/24.....	1	351	250.5	73.9	38.61	9.42	11		11.9	312.3	89	228.5	88.1 20.1 79.6
3/25.....	1	324	256.7	79.2	38.88	9.48	12		11.9	285.1	88	226.2	88.1 18.7 81.3
3/26.....	1	324	256.7	79.2	38.88	9.48	12		11.8	285.1	88	228.7	88.2 17 83
3/27.....	1	320	256.8	80.3	45.84	11.18	11.3		15.8	274.2	85.7	228.5	81.2 18 82
4/ 1.....	1	338	241	71.3	41.21	10.05	12.2		15.2	296.8	87.8	214.8	81.8 0.9 100
Aver. of five sleeping periods		331	255	77	40.7	9.90	12.3		14.3	290.3	87.7	225	86.7 11.8 85.2

TABLE 12.—SHOWING METABOLISM OF FOODSTUFFS ON HIGH PROTEIN FEEDING

Child Fed on High Protein Diet		Total Food Calories			In Food			Protein			Fat and Carbohydrate						
		Intake	Me- ta- bo- lized	Per Cent. of Intake	Calo- ries	Gm.	Per Cent. of Total	Calories	Gm.	Per Cent. of Total Food Intake	Metabolized		In Food		Metabolized		
											Calories Intake of F. & CH.	Per Cent. Derived From	Calories of Total	Per Cent. of Total	Calories Intake of F. & CH.	Per Cent. Derived From	
Day	Period																
2.....	1	448.1	290.35	58.1	74.6	18.2	16.7	40.75	9.2	56.4	15.6	372.5	83.3	219.6	58.8	0.0	100.0
6.....	1	327.3	253.43	86.6	49.1	12	15.1	36.13	8.1	73.6	12.7	278.1	84.9	247.3	81.0	43.2	56.8
8.....	1	297.7	253.89	85.3	62.3	14.7	21.0	38.49	8.6	61.7	15.2	225.4	79.0	215.4	91.5	0.0	100.0
10.....	1	310.7	243.92	78.4	135.9	33.1	43.7	80.13	18.0	59.0	32.8	174.8	56.3	163.8	93.8	0.0	100.0
10.....	2	310.7	309.2	100.0	135.9	33.1	43.7	80.13	18.0	59.0	25.0	174.8	56.3	240.1	137.0	74.8	25.2
10.....	3	310.7	362.93	117.0	135.9	33.1	43.7	80.13	18.0	59.0	25.0	174.8	56.3	282.8	162.0	88.9	11.1
13.....	1	306.8	300.5	100.0	169.3	41.3	56.2	84.66	19.0	50.0	28.1	131.5	43.8	215.9	164.0	0.0	100.0
13.....	2	306.8	306.0	102.0	169.3	41.3	56.3	84.66	19.0	50.0	27.7	131.5	43.8	221.4	168.0	52.5	40.5
13.....	3	306.8	347.8	115.0	169.3	41.3	56.2	84.66	19.0	50.0	24.3	131.5	43.8	263.2	200.0	100.0	0.0
12.....	3	353.9	362.9	102.0	177.4	45.3	50.1	83.99	18.0	47.3	23.1	176.5	49.9	278.8	159.0	100.0	0.0
Average ten periods.....		326.2	304.2	93.2	127.7	31.1	40.3	69.37	15.6	54.3	22.9	198.2	59.7	234.8	118.5	46.64	53.36

TABLE 13.—METABOLISM OF FOODSTUFFS

Total Food Calories				Protein			Fat and Carbohydrate									
In Food				Metabolized			In Food		Metabolized							
Intake	Me- ta- bo- lized	Per Cent. of Intake	Calo- ries	Gm.	Per Cent. Total	Calories	Gm.	Per Cent. Pro- tein Intake	Per Cent. of Total Food Intake	Calories of Total	Per Cent. of F. & OH.	Per Cent. Derived From				
Low protein diet, average of five sleeping hours.....	331	255	77.0	40.7	9.90	12.3	33.9	7.6	77.3	13.3	290.3	87.7	225	86.7	14.8	85.2
High protein diet, average of ten sleeping hours.....	326	304	93.2	127.7	31.1	40.3	69.37	15.6	54.3	22.9	198.2	59.7	224	113.5	46.5	53.4

In a study of the output of urinary nitrogen, Table 14, it will be interesting to note that during the low protein periods the average retention was 25.4 per cent. of the intake, while during the days on high protein feeding the retention was increased to 46.8 per cent. of the intake, which showed, therefore, a great relative as well as actual retention.

TABLE 14.—SHOWING NITROGEN RETENTION

Date	N in Food	N in Feces	N in Urine	N Retained	Per Cent. of Intake
3/24.....	1.507	.0922	0.924	.3450	22.9
3/25.....	1.509	.0920	1.008	.4090	27.0
3/26.....	1.509	.0926	1.008	.4090	27.0
1*.....	1.788	.1747	1.008	.5953	33.3
2.....	2.913	.2846	1.183	1.4454	49.6
3.....	1.381	.1350	.952	.294	21.3
4.....	1.775	.1734	.8946	.707	39.1
5.....	1.608	.1571	1.169	.2819	17.5
6.....	1.92	.1876	1.113	.6194	32.2
7.....	1.49	.1456	.995	.3494	23.4
8.....	2.3635	.2309	1.1556	.9770	41.3
9.....	3.382	.3303	1.7190	1.3327	39.1
10.....	5.204	.5182	2.367	2.4188	47.6
11.....	2.524	.3443	1.943	1.2367	35.0
12.....	6.925	.6766	2.347	3.9014	56.3
13.....	6.607	.6457	2.403	3.5583	53.8

\* Observation began. During the last five days of the series the feces were collected and analyzed and the nitrogen content was found to be 2.515 gm. or 0.977 per cent. of the nitrogen intake. The figures for the daily fecal nitrogen are calculated on this basis for entire period.

## CLINICAL IMPORTANCE OF FINDINGS

What is the clinical importance of the above findings? It is evident that greater attention should be paid to the relative and actual amount of protein in feeding formulas; particularly is this true in formulas made from whole milk, skimmed milk, buttermilk and albumin milk. Very frequently where there are signs of fermentation these formulas are fed without addition of sugar and the proportion of protein is relatively high. For example: When whole milk, or any of its dilutions, is fed without the addition of sugar, the percentage of calories arising from protein amounts to about 20 per cent.; when skimmed milk or its dilutions are fed without sugar, the protein calories amount to about 30 per cent.; when buttermilk (made from skimmed milk) is used, 40 per cent. of its calories are in the form of

protein; when the original Finkelstein's albumin milk is used having percentages of fat 2.5, carbohydrate 1.5 and protein 3.0 per cent., the proportion of calories due to protein is about 30 per cent. If, as is done both in this country and abroad, albumin milk is sometimes made up from fat-free curd, then the proportion of the protein in such fat-free albumin milk reaches as high as 43 per cent. Just in proportion as sugar is added, the relative percentage of protein calories is diminished as is shown in Table 15.

TABLE 15.—SHOWING RELATIVE DIMINUTION OF PROTEIN CALORIES WHEN SUGAR IS ADDED

	Per Cent. of Formula			Calories in		Per Cent. of Calories From		
	Fat	CH.	Protein	1 Oz.	1 Liter	Fat	Sugar	Protein
Albumin milk without sugar added .....	2.5	1.5	3.0	12.51	417	55.8	14.7	29.5
Albumin milk with 2% sugar added....	2.5	3.5	3.0	15.27	509	45.9	30.0	24.1
Albumin milk with 5% sugar added....	2.5	7.0	3.0	18.66	622	37.4	42.8	19.8
Albumin milk with 7% sugar added....	2.5	8.5	3.0	21.12	704	33.0	49.5	17.5
Albumin milk with 10% sugar added....	2.5	11.5	3.0	24.71	827	28.1	57.1	14.8

The facts as shown above for albumin milk are also true for other types of milk. In order to bring the proportion of calories derived from protein down to 7 per cent. of total, the amount of sugar added must be considerably increased. For example, for every ounce of whole milk (fat 3.5, carbohydrate 4.5, protein 3.5) used in a formula there should be one-third ounce of sugar added. For every ounce of the top half (7 per cent. fat) one-quarter ounce of sugar should be added. For every ounce of top third (10 per cent. fat) one-sixth ounce of milk sugar should be added.

#### HOW DETERMINE THE PROTEIN NEED

There have been several general rules applied for determining the protein need, all of which, in the light of these researches, give a higher proportion than is necessary to supply the actual need.

The rule followed pretty generally in this country is that an infant should receive the protein contained in an ounce or an ounce and a half of whole milk per pound weight of child.

Cowie<sup>15</sup> gives the accompanying table (Table 16) as covering the protein requirement.

15. Cowie: AM. JOUR. DIS. CHILD., 1912, iv, 360.

TABLE 16.—PROTEIN REQUIREMENTS

Age	Grams Protein Per		
	Kg.	Pound	Ounce
Two weeks.....	1.5	.68	.0425
Three weeks.....	2.0	.90	.056
Four weeks.....	2.5	1.10	.0687
Two to twelve months.....	2.5-3.3	1.10-1.5	.093

On the Continent a general rule is that one-tenth of the body weight should be given in whole milk. This, say in a child of 4,500 grams, would mean the protein of 450 c.c. of whole milk. This would require 15 ounces of whole milk. There are 4 calories from protein in each ounce of whole milk, so that a child weighing 4.5 kilos would receive 60 calories of protein. Estimating the total calories needed at 100 calories per kilo the protein supplied would amount to 15 per cent. of the total, which is more than twice the need. Not only is the protein too high according to these general rules, but from latest researches by Benedict and Talbot, by Murlin and Bailey<sup>16</sup> for new-born infants and Murlin and myself<sup>10</sup> for infants between 2 and 12 months, it would seem that the total energy metabolism of infants under 6 months is much lower than that of infants between 6 months and 1 year. Murlin and I<sup>10</sup> collected data showing that the average metabolism of fourteen infants up to and including 4 months of age was 35.4 calories per square meter per hour; the average of seven infants from 6 to 12 months inclusive was 41.9 calories per square meter per hour. Instead, therefore, of feeding 100 calories per kilo under 6 months, and from 70 to 80 calories per kilo from the sixth to twelfth month, the figures should be reversed and 70 or 80 calories per kilo should be fed under 6 months and 100 calories per kilo between 6 and 12 months. Further observations, however, should be made before such a radical change is recommended.

The protein need would therefore be much more nearly supplied if one-half the quantity outlined in these general rules were used, viz.,  $\frac{3}{4}$  of an ounce of skimmed, whole or top milk per pound weight of infant, or  $\frac{1}{20}$  of body weight in skimmed, whole or top milk. This coupled with the rules regarding the use of sugar would enable one easily to determine the need and supply it along with other food elements. Take for example a child weighing 12 pounds. Its protein need is supplied by  $\frac{3}{4}$  ounce of milk per pound; hence the child should

16. Murlin and Bailey: Proc. Soc. Exper. Biol. and Med., 1914, xi, 109.

receive 9 ounces of milk. If this were supplied in the form of whole milk it would be necessary to add to it 3 ounces of milk sugar (or sugar and starch) and diluent sufficient to supply its fluid need. In the 9 ounces of whole milk there would be 180 calories and in the 3 ounces of sugar and starch there would be 360 calories, making in all 540 calories, 36 of which are from protein. A child of 12 pounds needs about 540 calories daily; hence we have both its protein and its calories need supplied.

I have followed the method of feeding low protein for the past three years and it is my belief that children do better, since the method allows the giving of much larger quantities of carbohydrates and fats without overfeeding the child, and readily permits the use of top, whole, skimmed or buttermilk formulas according to the clinical indications of each individual infant. Where large quantities of milk are fed it is necessary to feed relatively low proportions of carbohydrates if one attempts at all to approximate the caloric need.

The foregoing statements are not intended to discourage the use of albumin milk or skimmed or buttermilk without additions of sugar over short periods of time when one desires to secure the therapeutic effect of a food relatively rich in protein and calcium for the purpose of controlling diarrheas, as outlined in an article by Wilcox and Hill.

It is also recognized that every child is a law unto itself in the matter of feeding; particularly is this true in its relation to fat and carbohydrate food, but it would seem that the supply of protein is a much more fixed quantity, since growth of tissue is much more dependent on it than on either fat or carbohydrate.

A series of clinical records are being collected covering cases fed on low protein and will be published separately.

#### SUMMARY OF FINDINGS

1. Protein when fed in excess of need causes an increase in the energy metabolism.
2. The increase is in proportion to the amount of protein oxidized, and not to the amount of protein added to the body.
3. Protein when fed in excess does not reduce the amount of fat and carbohydrate metabolized, but the fat and carbohydrate need remains fairly constant, and unless the minimal need of fat and carbohydrate is supplied in the food the organism will draw on its stored-up fat and glycogen to supply the difference between the amount fed and that which is metabolized.
4. When protein is fed greatly above its need it tends to produce a condition of stupor which assumes serious proportions if such feeding is continued. This stupor gradually disappears as protein is reduced in the diet. This condition is best considered as a protein food injury

and constitutes a clinical entity as definite in its symptomatology as that which arises from too prolonged use of a rich carbohydrate diet.

5. The protein need of the growing infant is supplied when 7 per cent. of its caloric need is furnished in protein calories.

6. A general rule which will approximate the protein need is to furnish  $\frac{3}{4}$  ounce of whole, skimmed or top milk, per pound weight of child, or if the metric system is applied,  $\frac{1}{20}$  of the body weight in skimmed, whole or top milk.

7. To keep the protein calories in any formula approximately 7 per cent. of the total, the following rule regarding the addition of sugar or cereal gruels or both may be followed: For each ounce of whole milk add  $\frac{1}{3}$  ounce of sugar or cereal.<sup>17</sup> For each ounce of top 16 ounces (7 per cent.) milk add  $\frac{1}{4}$  ounce of sugar or cereal. For each ounce of top 10 ounces (10 per cent.) milk add  $\frac{1}{6}$  ounce of sugar or cereal.

8. It is clearly recognized that rules outlined for feeding for nutritional purposes only cannot be followed when one feeds a food for therapeutic as well as nutritional purposes, hence the feeding of albumin or skimmed milk, i. e., a high protein food, is justified on the ground of its being a therapeutic measure and should be discontinued when the therapeutic indication no longer exists.

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17. The amount of cereal is estimated by the quantity of the dry cereal used in making the cereal diluent.

# STUDIES IN INFANT METABOLISM AND NUTRITION, V

UNDER THE DIRECTION OF L. EMMETT HOLT, M.D., AND  
D. D. VAN SLYKE, PH.D.

## *The Composition and Preparation of Protein Milk (Eiweissmilch)\**

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The value of protein milk in disturbances of infantile digestion is appreciated in this country only by the comparatively small number who have used it extensively. It has not yet found its way into general practice and it is in general use in only a few of our hospitals. Many have been deterred from prescribing it owing to the difficulties in preparation as originally published. Much regarding the use of protein milk has been brought out since Finkelstein's original publication in 1910. A simplification and standardization of the method of preparation seems therefore desirable.

Not only a variation in the ingredients used but also the methods employed make noteworthy differences in the composition of the product. To these variations some of the differences in the results are no doubt due. Examination showed that samples of protein milk made in the same diet kitchen by the same nurse and with the same materials differed so widely, especially with respect to the fat content, that a careful study was undertaken to ascertain the effect of the different steps of preparation on the final product and to discover the explanation of these variations.

Finkelstein's<sup>1</sup> original method of preparation as described by him in his early publication is briefly as follows:

To one liter of milk, one teaspoonful of rennet is added. This is then allowed to stand in a water bath at 42 C. for one-half hour. It is then placed in a linen bag and the whey strained off by suspending this for one hour. The curd is rubbed once or twice through a fine sieve with the addition of one-half liter of water, and one-half liter of buttermilk is then added.

The original milk used contained: fat, 3.5; sugar, 4.5; protein, 3.0; ash, 0.70  
The protein milk contained: fat, 2.5; sugar, 1.5; protein, 3.0; ash, 0.50

According to Finkelstein, the beneficial effects of protein milk were due to (1) its low sugar; (2) the dilution of the whey; (3) the high

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\* From the Laboratories of the Rockefeller Institute for Medical Research and the Babies' Hospital.

1. Finkelstein and Meyer: Jahrb. f. Kinderh., 1910, lxxi, 525.



casein; (4) a combination of relatively high fat and high calcium, this favoring the production of formed stools.

Protein milk has been frequently described as a food low in salts; in fact, many writers have laid stress on the great reduction of the salts as one of the advantages of protein milk.<sup>2</sup> Rollet<sup>3</sup> proceeds on the assumption that it contains only the salts of the buttermilk which, according to Finkelstein's method of preparation, constitute one-half the fluid volume. Such, however, is not the case. In Finkelstein's and Meyer's own analyses the total salt content is five-sevenths of that of the original milk. But the proportion of the different salts is not the same as in whole milk; while the proportion of the soluble salts is reduced, that of the insoluble salts is increased.

Our analyses, which were first made in connection with metabolism studies, have always shown considerably higher values than those of Finkelstein and Meyer, not only for the total ash but for most of the ash constituents. This may have been in part due to the method of preparation which differed slightly from that of Finkelstein.

In the first place, in order to reduce the sugar content as much as possible, after the whey has been strained off we have washed the curd in sterile water. This was believed not only to reduce the sugar but also the salt content. The extent to which this is accomplished is shown in the analyses given in the subsequent tables.

Again, instead of adding one-half liter of water and one-half liter of buttermilk to the washed curd, only enough water was added to bring the final volume up to one liter, the difference being about 100 to 120 c.c. of water which is displaced by the curd.

Finally, instead of the usual commercial buttermilk which contained about 4 per cent. of sugar, we used a specially fermented milk with but 3.5 per cent. sugar. This, moreover, was never fat-free but contained on the average 0.5 per cent. of fat; besides, there had been added a small amount of table salt. Our analyses showed, therefore, a higher NaCl content than that reported by Finkelstein.

*Variations in the Fat.*—Since samples of protein milk examined on three successive days gave the fat content as 2.2, 3.5 and 3.1 per cent., respectively, there were evidently conditions in the method of preparation which influenced the final product in an important way, and it was the purpose of our investigation to find out what these were, and to devise a method which reduced these variations to the minimum.

The causes of variation were apparently dependent on at least three different factors, any one of which might influence the per-

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2. Leopold: Arch. Pediat., 1910, p. 602.

3. Rollet: Berlin Klin. Wehnschr., 1911, p. 835.

centage composition of the product, viz., (1) The percentage composition of the ingredients used. Although purchased from a large dealer the variation in the fat percentage in the whole milk from day to day was found to be over 0.5 per cent. (2) The conditions under which the curd was formed seemed important—the temperature, the time of standing, the amount of rennet added, the amount of the protein milk made at one time, etc. (3) The manner of manipulation in the straining, the washing of the curd and in the rubbing through the sieve, all had an effect on the composition of the product.

In order to decide these questions protein milk was made under varying conditions. It was prepared in different quantities varying from 1 to 10 liters at a time; the amounts of the elements used were accurately measured as well as the quantity of the final product. Complete analyses were made of the ingredients used—the milk, the buttermilk and the junket tablets; of the waste products—whey and washings; and of the final product, the protein milk. Analyses of the fat were made many times, this being the constituent which varied most. A smaller number were made of the protein, sugar and salts. It soon became evident that the chief causes of variation were to be found in conditions which affected the firmness of the curd. A firm curd held the fat more closely bound, and neither the fat nor the casein passed through the gauze in any appreciable amount; while if the curd was soft, a considerable amount of both fat and casein were lost in the whey.

The routine procedure followed in the hospital diet kitchen was found to be as follows:

A quantity of whole milk, usually eight or ten liters, was heated to about 100 F. and into it was gently stirred for a moment one junket tablet, dissolved in a small amount of water, for each liter of milk. The milk was left standing, covered, at the temperature of the room, usually about 72 F., for thirty or forty minutes. It was then poured on two thicknesses of cheese cloth, by tilting which the curd was gently rolled from side to side and the whey drained away in the course of eight or ten minutes. Water was then poured on the curd and the manipulation repeated. This washing was done twice. The curd was then placed on a fine wire sieve, fifty meshes to the inch, and rubbed through it with a metal vegetable masher, with the gradual addition of one-half liter of buttermilk to each liter of whole milk used for the curd. Enough water was then added to make the volume equal to that of the original milk.

It had long been a tradition of the diet kitchen that "good protein milk" could not be made from so small an amount as one or two liters made from one or two liters was far below the average in fat content, as can be seen from the following experiments.

From one lot of whole milk containing 3.3 per cent. fat, one-liter and four-liter samples were taken; from another lot containing 3.5 per cent. fat, one-liter, two-liter and four-liter samples were taken.

Protein milk was made from each of these samples, the condition being kept as nearly as possible the same for all. The results are given in Table 1.

The figures showed extraordinary variation in the fat. That made from the first lot showed in the one-liter sample 2.15 per cent. fat; in the four-liter sample, 2.70 per cent. fat. In the second lot, the one-liter sample gave 1 per cent. fat; the two-liter, 1.6 per cent.; the four-liter sample, 2.37 per cent. (Vide analyses 1 to 5, Table 1.) In two ten-liter samples (Nos. 6 and 7) made from milk containing 3.6 per cent. fat the fat in the product was respectively 2.34 and 2.90 per cent. It would appear from this that the percentage of fat in the product is distinctly lower if only one or two liters, instead of a larger amount of milk, is used; but that above this quantity the exact amount used is not important.

The reasons for the difference between large and small quantities seemed to be two: A certain amount of the fat always adhered to the cheese cloth. In the one-liter samples the proportion of this to the whole amount of fat was considerable, while in the large samples the proportion to the whole was small. Again, in the manipulation of the curd used to remove the whey, the small curd broke apart more readily than the large curd, and consequently a larger proportion of the fat and casein were lost in the whey and in the washing. This made it clear that a method of removing the whey which involved less manipulation of the curd would insure a more uniform product and higher percentage of fat and of protein. This was demonstrated to be the case by the following experiments:

Two four-liter samples were measured from the same milk. The curd from one was handled in the usual way. That from the other was drained by suspension for two hours, the procedure in other respects being the same in both cases. From each of two other lots of milk three three-liter samples were taken. The curd in one sample in each group was drained by manipulating the gauze in the usual manner; that of another was suspended ten minutes and then manipulated till dry; that of the third was suspended for two hours without any manipulation. (Vide analyses 8 to 15, Table 1.)

In general these observations showed that the less the curd is manipulated in removing the whey, the higher the percentage of fat in the protein milk.<sup>4</sup> Of the four-liter samples the one in which the whey was removed by suspension showed 3.5 per cent., while the one

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4. These experiments have proceeded on the assumption that a low fat was not generally desired in protein milk. The hospital experience has been that one of its chief advantages is its rather high fat content. However, should one wish to secure a low fat with high casein, skimmed milk, instead of whole milk, should be used in its preparation.

TABLE 1.—VARIATION IN FAT OF PROTEIN MILK DUE TO DIFFERENCES IN QUANTITY PREPARED AND TO DIFFERENT METHODS OF HANDLING

No.	Quantity of Milk Used for Curd, cc.	Method of Draining Whey from Curd	Grams in Milk Per Liter	Grams in Whey Per Liter	Grams in Wash Per Liter	Grams in Curd (by Subtraction)	Per Cent. of Amount in Milk in Curd	Grams in Buttermilk Per Half-Liter	Grams in Protein * Milk Per Liter (By Estimation)	Grams in Protein * Milk Per Liter (By Determination)
1	1,000	Entirely drained by handing in cheese cloth	33	8.36	6.50	18.14	55.0	4.0	22.14	21.50 †
2	4,000	Same	33	4.61	4.74	23.65	71.7	4.0	27.65	27.00
3	1,000	Same	35	18.25	7.00	9.75	27.9	5.5	15.25	10.00
4	2,000	Same	35	16.17	2.60	16.23	46.4	5.5	21.73	16.00
5	4,000	Same	35	12.28	1.73	20.99	60.0	5.5	26.49	23.70
6	10,000	Same	36	11.57	2.31	22.12	61.4	3.5	25.62	23.40
7	10,000	Same	36	9.00	.99	26.01	72.2	3.5	29.51	29.00
8	4,000	Same	35	19.26	2.40	13.34	38.1	4.0	17.34	11.00
9	4,000	Drained by suspending 2 hours	35	3.20	†	31.80	90.9	4.0	35.8	35.00
10	3,000	Drained entirely by handing	35	12.91	1.26	20.83	59.5	4.5	25.33	24.00
11	3,000	Drained 10 minutes by suspension; rest by handing	35	6.35	1.73	26.92	76.9	4.5	31.42	31.00
12	3,000	Drained by suspending 2 hrs.	35	2.96	2.27	29.77	85.0	4.5	34.27	34.00
13	3,000	Drained entirely by handing	31	8.23	1.20	21.57	69.6	3.5	25.07	24.50
14	3,000	Drained 10 min. by suspension; rest by handing	31	5.31	.99	24.70	79.7	3.5	28.20	28.00
15	3,000	Drained by suspending 2 hours	31	2.99	2.86	25.15	81.1	3.5	28.65	25.50
16	2,000	Drained by resting on sieve 10 minutes, then by handing	30	6.36	1.68	21.96	73.2	3.5	25.46	25.00

\* The amount of fat by estimation is necessarily higher than that obtained by determination because of the amount lost on utensils.

† The figures given in this column show the grams per liter; the per cent. is obviously one-tenth of this. ‡ By mistake this curd was not washed.

manipulated showed but 1.1 per cent. One of the three-liter series gave the following values: Fat in sample suspended two hours, 3.4 per cent.; fat in sample suspended ten minutes and then manipulated, 3.1 per cent.; fat in sample manipulated without suspension, 2.4 per cent. The other series gave similar results. The apparent exception will be referred to later.

As a result of these observations the following procedure was adopted:

The whole milk is coagulated as above described. After standing for thirty minutes the coagulum is poured on a doubled piece of ordinary cheese-cloth and allowed to remain for fifteen minutes, the cloth resting on the sieve through which the curd is later to be pressed. The cheese-cloth is then gently manipulated for a few minutes to complete the removal of the whey. The curd is now washed twice, using each time about one-fifth as much water as the original amount of milk taken. The water is poured on the curd, which is then gently manipulated for two or three minutes. The curd is then transferred to the sieve and pressed through it with the gradual addition of half as much buttermilk as the volume of whole milk taken. Boiled water is then added to make the volume equal to that of the original milk used. Great care must be taken in pressing the curd through the sieve lest the fat be transformed into butter, which often adheres to the sides of the utensils or floats on the surface of the milk. This is avoided by rubbing gently in one direction, the rotary motion being almost certain to form butter. A fat determination in such a sample is manifestly unreliable. (Vide analysis 15, Table 1.)<sup>5</sup>

A series of over thirty observations (Table 2) was carried out to determine to what extent uniformity of fat content was secured with the method of handling the curd just described. On successive days samples of the original milk, the buttermilk and the protein milk were analyzed for fat. In protein milk made from the same milk supply by different persons there was a great variation in the amount of fat retained; it ranged between 52 and 86 per cent. of the fat in the original milk. (Vide analyses 1 and 2, Table 2.) When made by a single experienced person, not only was the fat in the protein milk more nearly uniform but the actual loss of fat was much less. In one instance, the range of fat retained was from 86 to 97 per cent. of the fat in the milk; in another, 76 to 79 per cent.; in a third, 93 to 97 per cent. (Vide analyses 3 to 5, Table 2.)

From these figures the proportion of the fat of the whole milk retained in the curd and consequently in the protein milk is easily estimated. With proper handling fully four-fifths of the fat of the whole milk used is retained in the protein milk. But the total fat of the protein milk contains also a small amount of fat in the buttermilk. If commercial buttermilk is used, however, this is a negligible quantity.

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5. The loss of fat in whey and washings indicates that the fat value of the protein milk is too low.

TABLE 2.—VARIATIONS IN THE FAT OF PROTEIN MILK WHEN PREPARED ACCORDING TO A PROPER METHOD, BY DIFFERENT PERSONS

No.	No. of Determinations Considered	By Whom Prepared	Range of Fat Percentage in Whole Milk Used	Average Per Cent. of Fat of Whole Milk	Range of Fat Percentage in Buttermilk Used	Average Per Cent. of Fat of Buttermilk	Range of Fat Percentage of Protein Milk	Average Per Cent. of Fat of Protein Milk	Range of Per Cent. of Whole Milk Fat Held in Curd	Average Per Cent. of Whole Milk Fat Held
1	10	Prepared by various persons	3.00-3.65	3.37	0.35-0.75	0.55	2.45-3.35	2.78	61-86	74.2
2	10	Prepared by various persons	3.15-3.40	3.29	0.40-1.70	0.68	1.95-3.35	2.76	52-83	73.6
3	6	Prepared by Nurse A	3.00-3.30	3.10	0.5 -0.6	0.57	3.0 -3.20	3.09	86-97	90.6
4	4	Prepared by Nurse B	3.00-3.90	3.44	0.65-0.90	0.79	2.65-3.90	3.08	76-79	78.0
5	2	Prepared by Nurse C	3.00-3.00	3.0	0.8 -0.8	0.80	3.20-3.30	3.25	93-97	95.0

TABLE 3.—AVERAGE COMPOSITION (FAT, SUGAR, PROTEIN, TOTAL ASH) OF PROTEIN MILK, OF THE INGREDIENTS USED, AND OF THE WHEY AND THE WASH (FROM FIVE ANALYSES)

	Grams in Milk Per Liter	Grams in Whey Per Liter	Grams in Wash Per Liter	Grams in Curd (by Subtraction)	Per Cent. of Amount in Original Milk in Curd	Grams in Buttermilk Per Half-Liter	Grams in Protein * Milk Per Liter (By Estimation)	Grams in Protein * Milk Per Liter (By Determination)
Fat .....	34.0	5.65	2.14	26.21	77.1	4.0	30.21	29.8
Sugar .....	46.7	41.53	4.89	0.28	0.6	18.06	18.34	22.0
Protein .....	31.9	7.71	1.62	22.57	70.8	15.36	37.93	37.5
Total Ash.....	7.944†	4.751	0.597	2.586	32.6	4.034	6.620	6.528

\* The values for the ingredients of protein milk obtained by estimation are necessarily greater than those obtained by determination because of the amount lost on utensils.

† The salt of the junket tablets used in coagulating the milk is included in the total ash of the milk.

Consideration of the figures given in the foregoing table forces one to the conclusion that a very important factor in insuring a uniform fat in protein milk is the care used in the various steps of the operation.

The method of preparation which has been described above is the one to be recommended where considerable quantities of protein milk are to be made at one time, as for hospital use. If only one or two liters are desired, or it is to be made by an inexperienced person, the chances of error are much less if all the whey is drained away by suspension of the curd.

The other constituents—sugar, protein and salts—as has been already suggested, vary much less than does the fat.

*The Sugar.*—The sugar content of the original milk used ranged from 4.5 to 4.8, the average being 4.7 per cent. When the protein milk is properly made there is removed in the whey and in the washing nearly all the sugar of the original milk. On the average, about nine-tenths of what is removed comes out in the whey, and one-tenth, in the washing. The percentage of sugar in the protein milk should therefore be only about one-half that in the buttermilk. The figure for sugar in all our analyses was obtained by the reduction method. Owing to the difficulty of removing the protein from the protein milk before determining the sugar value, the figure for sugar is probably too high. Our average sugar figure in protein milk made under proper conditions is about 2 per cent. This figure is obtained from a larger number of determinations than are included in Table 3. The apparent error, assuming the curd to be nearly sugar-free, is therefore, 0.2 per cent. The actual sugar content of protein milk carefully prepared, as above described, must average about 2 per cent., using commercial buttermilk, or a little less than 1.8 per cent., using the specially fermented milk.

*The Protein.*—The percentage of protein in the protein milk is influenced by the same conditions as those which affect the fat, but to a less degree. The protein of the whole milk used averaged 3.25 per cent. When properly made there is lost in the whey 0.77 per cent.; in the washings, 0.16 per cent. Besides the lactalbumin, this must include some of the casein mechanically carried through. Some is also left on the utensils. The protein of the buttermilk used averaged 3.07 per cent. The total percentage of protein of the product would be half this (since the buttermilk represents one-half the volume) plus the curd protein which, after deducting the loss in the whey and the waste, leaves about 2.26 per cent. of the original milk. By addition this would make the protein content of the protein milk 3.79 per cent.; by determination it was 3.75; the range being 3.60 to 4.00 per cent. Of this protein only about 0.25 is lactalbumin, about 3.50 being casein.

TABLE 4.—DISTRIBUTION OF THE SALTS OF THE ASH OF PROTEIN MILK. OF THE INGREDIENTS USED, AND OF THE WHEY AND THE WASH (FROM FIVE ANALYSES)

	Grams in Milk Per Liter	Grams in Whey Per Liter	Grams in Wash Per Liter	Grams in Curd (by Subtraction)	Per Cent. of Amount in Original Milk in Curd	Grams in Buttermilk Per Half-Liter	Grams in Protein * Milk Per Liter (By Estimation)	Grams in Protein * Milk Per Liter (By Determination)
CaO .....	1.757	0.486	0.108	1.163	66.2	0.833	1.996	1.930
MgO .....	0.199	0.101	0.015	0.083	41.7	0.104	0.187	0.180
P <sub>2</sub> O <sub>5</sub> .....	2.060	0.796	0.140	1.124	54.6	1.024	2.148	2.121
K <sub>2</sub> O .....	1.887	1.514	0.167	0.206	10.9	0.828	1.034	1.028
Na <sub>2</sub> O .....	0.770†	0.636	0.070	0.064	8.3	0.511	0.575	0.563
Cl .....	1.420†	1.148	0.120	0.152	10.7	0.764	0.916	0.868

\* The values for the ingredients of protein milk obtained by estimation are necessarily greater than those obtained by determination because of the amount lost on utensils.

† The NaCl of the junket tablets is included in that of the milk.

TABLE 5.—COMPARISON OF THE SALTS OF DIFFERENT MILKS

	Total Ash, Per Cent.	CaO	MgO	P <sub>2</sub> O <sub>5</sub>	K <sub>2</sub> O	Na <sub>2</sub> O	Cl
Protein milk (12 analyses)	0.648 *	0.201	0.021	0.222	0.109	0.032 *	0.061 *
Cow's milk (5 analyses)	0.743	0.176	0.020	0.206	0.189	0.050	0.111
Woman's milk (16 analyses of normal mature milk)	0.206	0.047	0.008	0.034	0.057	0.014	0.035

\* This figure is obtained after subtracting for the NaCl added to buttermilk used in our experiments.



By the method of preparation—precipitation and mechanical subdivision—this large amount of casein is readily held in suspension and passes through the ordinary rubber nipple. If carefully warmed for feeding this suspension is not interfered with. But owing to the acidity of the milk any considerable degree of heat causes a separation and precipitation of the casein in large masses.

*The Salts.*—So much has been said of the salts in the literature of protein milk that the total salts and the distribution of the salts were made a subject of special study. In general it was found, as was anticipated, that the soluble salts of the original milk were largely removed in the whey and in the washings, while a large part of the insoluble salts was retained in the curd.

There is retained in the curd	62.5	per cent. of the	CaO	of the whole milk
" " " "	39.9	" " "	MgO	" " "
" " " "	53.5	" " "	P <sub>2</sub> O <sub>5</sub>	" " "
" " " "	10.7	" " "	K <sub>2</sub> O	" " "
" " " "	6.4	" " "	Na <sub>2</sub> O	" " "
" " " "	7.2	" " "	Cl	" " "

The salts of the final product will therefore be the salts of the buttermilk plus those retained in the curd. In Table 4 is shown the quantity of each of the salts in the milk and buttermilk used, also the amount removed in the whey and the washings and the amount present in the protein milk.

In Table 5 is shown the salts of protein milk compared with those of cow's milk and woman's milk.

It will be noted that the proportion of CaO and P<sub>2</sub>O<sub>5</sub> in protein milk is slightly higher than in cow's milk while that of MgO is practically the same in both. A reduction is seen only in K<sub>2</sub>O, Na<sub>2</sub>O and Cl, the amount of which is but little over half as great as in whole milk.

As compared with woman's milk, not only are the total salts of the ash in great excess, but the amount of calcium is nearly five times, and the phosphorus, nearly seven times as great. The soluble salts also are nearly twice as abundant in protein milk.

To the large excess of insoluble salts, especially calcium, is no doubt to be ascribed the value of protein milk in producing formed stools.

From these observations there is found no basis for the statement that protein milk is low in salts, since it contains not only a higher total ash, but higher amount of all the different salts than are ordinarily given to infants artificially fed. Even when protein milk is diluted, the amounts are much greater than nursing infants receive. The advantages of its use cannot therefore be attributed to the amount of salts removed, nor can the failure to gain weight be ascribed to the absence of the usual salts of the whey. The lowering of the Na<sub>2</sub>O

and Cl in the preparation of the protein milk seems to be of no special advantage. As used in the Babies' Hospital extensively for three years with most satisfactory results, it has contained, owing to the addition of NaCl to the buttermilk used, an amount of these elements nearly as great as in cow's milk and much greater than that in woman's milk.

#### CONCLUSIONS

1. The chief variation in the composition of protein milk is in the fat. Uniformity is secured not only by the use of ingredients of uniform composition, but, what is much more important, by the exercise of great care in the handling of the curd. It should be suspended for a short time or allowed to rest for fifteen minutes on the sieve before manipulation to drain off the whey; care in pressing the curd through the sieve is also essential.

2. Since the value of protein milk is in large measure due to its low sugar content, the washing of the curd with water is a useful means of removing an additional amount of sugar.

3. When properly prepared the amount of protein in protein milk is quite constant and is usually somewhat greater than that of the original milk; it is nearly all casein.

4. If the buttermilk is added while the curd is being rubbed through the sieve, it is unnecessary to repeat this part of the process.

5. In the ash of protein milk the amount of calcium and phosphorus is slightly greater, that of sodium, potassium and chlorine is less than in whole milk, being reduced to a little more than one-half the proportion present.

6. Certain things are to be avoided in preparing protein milk: (1) stirring too much or too long while adding the rennin; (2) leaving the milk during curd formation in a cold place; (3) any unnecessary handling of the curd in straining off the whey or in washing or in pressing through the sieve; (4) subsequent heating beyond that required in feeding.

7. The composition of protein milk obtained from all our analyses when made as above described is: Fat, 3.0 to 3.50 per cent.; sugar, 1.8 to 2.0; protein, 3.60 to 4.00; ash, 0.65.

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## THE DIAGNOSTIC SIGNIFICANCE OF D'ESPINE'S SIGN \*

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"The duration of pulmonary consumption in children varies; but it is generally more rapid with them than with adults, as in a large proportion of cases the tubercular disease commences in young subjects in the bronchial glands, and remains often for a considerable time unnoticed especially when unattended by a cough. The length of time during which tuberculization may have been proceeding before it is discovered is generally very uncertain. The suppuration or softening of tubercles in the bronchial glands very rarely occurs without corresponding diseases afterwards appearing in some parts of the lungs, which affords all the characteristic symptoms of pulmonary phthisis. The disease has, however, proved fatal, having been accompanied with decided hectic fever, when the bronchial glands alone have been found to be the seat of the malady." So wrote Coley<sup>1</sup> in 1846.

Nevertheless it was not until within comparatively recent years that it was deemed possible by means of physical signs to detect their enlargement, so deeply do they lie within the thoracic cavity. In 1907 D'Espine<sup>2</sup> drew attention to a sign that he had observed for many years and considered diagnostic of enlargement of these glands. He stated that in young children the whispered voice normally ceases at the level of the seventh cervical spine posteriorly. When, however, there is enlargement of the lymph nodes and the patient whispers "three thirty three" bronchophony is heard over the upper thoracic spine as well. Although considerable evidence has been brought forward in support of D'Espine's contention, clinicians are far from agreeing as to its real value, many disregard it entirely. In an article dealing with tuberculosis in children Landis<sup>3</sup> makes no mention of D'Espine's sign or of increased whisper in the interscapular space. He does, however, express the opinion that percussion of this region is unreliable for the detection of glandular enlargement.

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1. Coley: A Practical Treatise on the Diseases of Children, Jas. Milman, 1846.

2. D'Espine: Bull. de l'Acad. de méd., Paris, 1907, lvii, 167.

3. Landis: Am. Jour. Med. Sc., 1914, cxlviii, 530.

Manges<sup>4</sup> in an article dealing with the value of the whispered voice in detection of small areas of consolidation in the lung makes no mention of D'Espine's observations, and apparently he does not consider the whispered voice of especial significance over the hilum region, as he believes that "normally in a number of individuals the whispered bronchial voice can be heard distinctly, especially in children . . . near the large bronchi." In England the import of whispered bronchophony in detecting enlargement of the bronchial glands does not appear to be appreciated. Ewart, long an advocate of spinal percussion and more recently of paravertebral percussion, appears to ignore it completely.

Riviere<sup>5</sup> refers to D'Espine's sign, but he is of the opinion that percussion gives the more trustworthy results. Percy Kidd<sup>6</sup> also gave an adverse report, but as he counted the test positive in adults when heard only as low as the first and second thoracic spines, this criticism loses its weight.

Lees<sup>7</sup> reporting four cases of incipient pulmonary tuberculosis in children recently, refers to dullness over the hilum and to "deficient air entry" in the affected region, but one looks in vain for any statement as to the character and area of transmission of the whispered voice.

In an article dealing with hilum tuberculosis in children, Cullen<sup>8</sup> dismisses the physical signs with the statement that "pressure signs and symptoms occupy many pages of textbooks; in practice they may be safely disregarded."

Jordan<sup>9</sup> of Guy's Hospital seems to share the same view as to the utter untrustworthiness of all physical signs, for he tells us that "the only known method of making a diagnosis of peribronchial phthisis is the Roentgen method." "Radiography holds the field alone," he asserts.

On the other hand, Dautwitz<sup>10</sup> in a most exhaustive article extolling the value of physical signs in the detection of hilum tuberculosis expresses the opinion that whispered bronchophony is unquestionably of the most value, though he holds light percussion in high esteem. With this opinion Gesteira<sup>11</sup> of Rio de Janeiro agrees. He asserts

4. Manges, M.: *Tr. Am. Climat. Assn.*, 1912, xxviii, 132.

5. Riviere, Clive: *Early Diagnosis of Tubercle*, New York, Oxford University Press, 1914.

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7. Lees, D. B.: *Practitioner*, London, 1915, xciv, 373.

8. Cullen, J. P.: *Practitioner*, London, 1915, xciv, 610.

9. Jordan, A. C.: *Practitioner*, London, 1912, lxxxviii, 248.

10. Dautwitz: *Beihefte z. med. Klin.*, 1908, iv, No. 9.

11. Gesteira, J. M.: *Brazil Med.*, 1913, xxvii, Nos. 2 and 3; *Abstr. in Jour. Am. Med. Assn.*, 1913, lx, 873.

that in Brazil, D'Espine's sign is regarded "as the most reliable and easiest to apply of all means for revealing the presence of tuberculous processes in the tracheobronchial lymphnodes."

Zabel<sup>12</sup> also holds this sign in high esteem, as he often found it the only sign pointing to abnormality of the bronchial glands. He mentions a number of clinicians (Bard, Leroux, Krautz, Roch) who are of the same opinion.

Smith and Sweet<sup>13</sup> examined one hundred patients; the twenty who showed dulness at the lung root in each instance gave a positive D'Espine sign and a hilum lesion was revealed by the Roentgen ray.

Seventy cases of the one hundred exhibited a positive D'Espine's sign and of those 92.8 per cent. had positive Roentgen-ray findings.

Smith and Sweet concluded that except in rare instances a positive D'Espine's sign means enlarged bronchial glands. Occasionally owing to the situation of the glands, the whispered voice may not be detected, even in the presence of glandular enlargement as revealed by the Roentgen ray.

I have been interested in this question for several years.<sup>14</sup> Not only have I been able to compare the physical signs with the Roentgen-ray negative in a considerable series of cases, but several times I have observed the whisper grow markedly less over a period of several months as the general condition of the patient improved. Roch<sup>15</sup> noted the same thing in an adult with enlargement of both cervical and bronchial glands.

The control of these signs by necropsy does not appear to be very large. In a number of instances D'Espine has demonstrated glandular enlargement; and Smith and Sweet,<sup>13</sup> found a marked enlargement in one case which had exhibited a positive sign.

I have had a limited opportunity to compare these signs with the postmortem findings. In a few cases not presenting any increased whisper, no enlargement of the bronchial glands was found. Four exhibited a marked D'Espine and all had large bronchial glands.

The last case, that of a girl of 10 years, was of especial interest as the patient had been under close observation for a number of months and had a Roentgen ray taken shortly after the onset of her illness. She was referred to me by Dr. Walter G. Murphy in August, 1912, because of marked enlargement of the cervical glands. Her mother stated that she seemed extremely tired—too tired to play in

12. Zabel: *München Med. Wchnschr.*, 1912, lix, No. 49; Abstr. in *Jour. Am. Med. Assn.*, 1913, ix, 250.

13. Smith and Sweet: *AM. JOUR. DIS. CHILD.*, 1914, viii, 228.

14. Stoll, H. F.: *Am. Jour. Med. Sc.*, 1911, cxli, 83; *Am. Jour. Med. Sc.*, 1914, cxlviii, 369; *AM. JOUR. DIS. CHILD.*, 1912, iv, 333; *Boston Med. and Surg. Jour.*, 1912, clxvii, 291.

15. Roch: *Semaine méd.*, 1911. xxxi. 85.

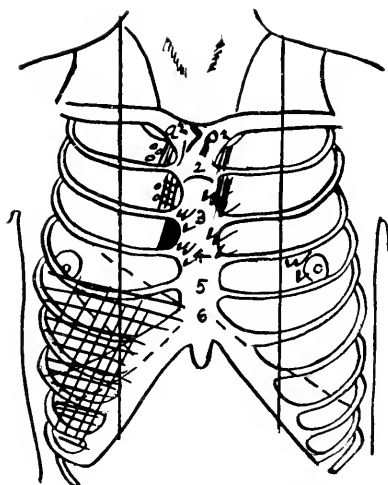


Fig. 1.—Breath sounds faint everywhere; ooo = râles; shaded area = impaired resonance; wv= whispered voice. Noteworthy point: 1, marked dulness, third space; 2, accentuated aortic second sound; 3, whispered voice along border of sternum. Compare with situation of glands D, D<sup>1</sup>, E, Figure 3.

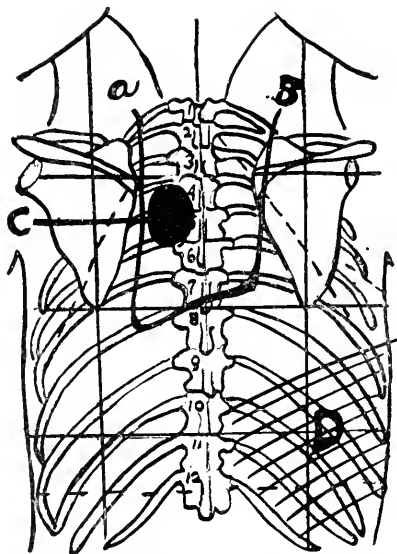


Fig. 2.—Line A-B shows area where whispered bronchophony was present; C, site of more marked whisper. (Compare with C, Figure 4) D, dulness—distant breath sounds.

fact—and her appetite was very poor. It is especially noteworthy that she had no cough at this time. The glands were so large, hard and discrete that Hodgkin's disease was considered but the microscopic examination of two of the glands showed them to be tuberculous. The intradermic tuberculin test was positive, leukocytes, 5,600. From the physical signs (Figs. 1 and 2) the diagnosis was made of enlarged bronchial glands, early involvement of right upper lobe—inner aspect

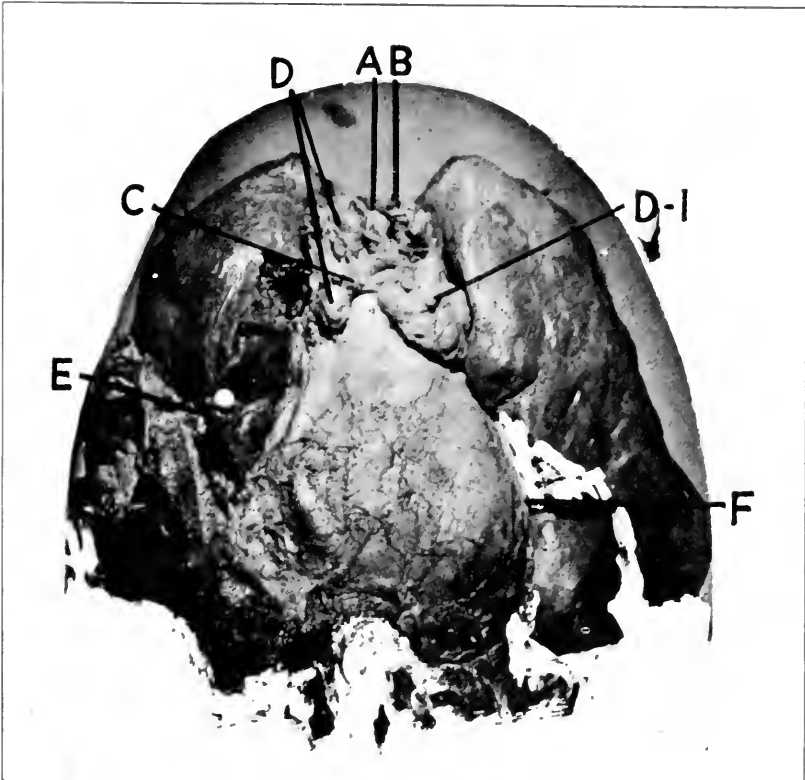


Fig. 3.—Thoracic viscera, anterior view; pericardium intact. *A*, trachea; *B*, left common carotid artery; *C*, junction of innominate veins; *D* and *D-I*, enlarged lymph glands; *E*, enlarged lymph gland just beneath the pleura (lung held back by pin); *F*, left phrenic nerve. Just below the line from *C* the lung has been incised to show the advanced tuberculous process just above the right bronchus. The inter-position of glands *D* and *D-I* between the aorta and chest wall explain the accentuation of the aortic second sound.

—with either a thickened pleura or a slight effusion at the right base. The Roentgen ray, taken a few weeks later, shows extensive disease at the (Fig. 5, *c*) right root. This was the location of the most advanced lesion at the necropsy (note the lung under line *C*, Fig. 3). Because

of the peribronchial tuberculosis, tuberculin treatment seemed preferable to excision of the cervical glands.

After about six months of improvement, she gradually failed as the lesion in the right lung slowly advanced. At the time of her death, about eighteen months after first coming under observation, there was marked softening anteriorly below the right apex, inner half and above the inferior angle of the right scapula posteriorly.

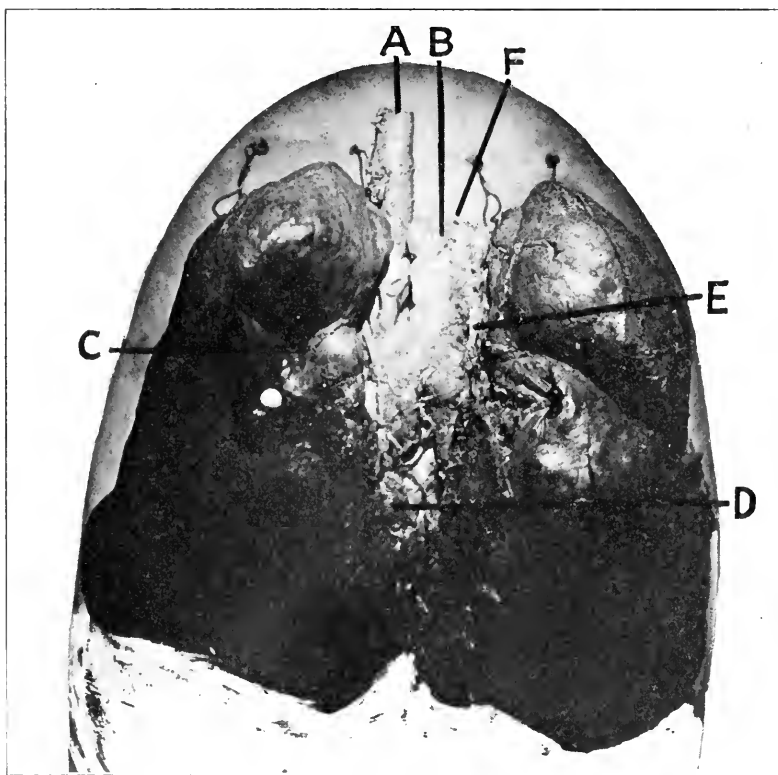


Fig. 4.—Posterior view thoracic contents. Aorta (*A*) has been dissected up in order to give a better exposure; *B*, trachea; *C*, very large gland between the lobes, just above the left bronchus. Internal to this gland the left vagus nerve is seen crossing the bronchus; *D*, the lower one of a chain of glands extending downward between the lower lobes; *E*, right vagus; *F*, right common carotid.

Throughout all the time the child was under observation, whispered bronchophony was present throughout the interscapular space and was always most marked to the left of the midthoracic vertebrae, and at the necropsy this area was directly over the enlarged gland between the left lobes. This fact, together with the diminishing of the whispered voice along the right side of the vertebrae, coincidental with the



development of the signs of pulmonary involvement, leads to the conclusion that it is the gland mass that plays the important part in the increase of the whispered voice.

It was never possible to elicit intrascapular dulness in the case of Helen A., until the signs of pulmonary involvement were evident. This probably was due in part to the fact that the largest gland posteriorly lay well to the left of the tracheal bifurcation about on a line with the vertebral border of the scapula. The impairment of the percussion note anteriorly was due to enlarged glands of the anterior mediastinum rather than to bronchial glands. Dulness anteriorly in children is usually due to an enlarged thymus, especially when most marked to the left.

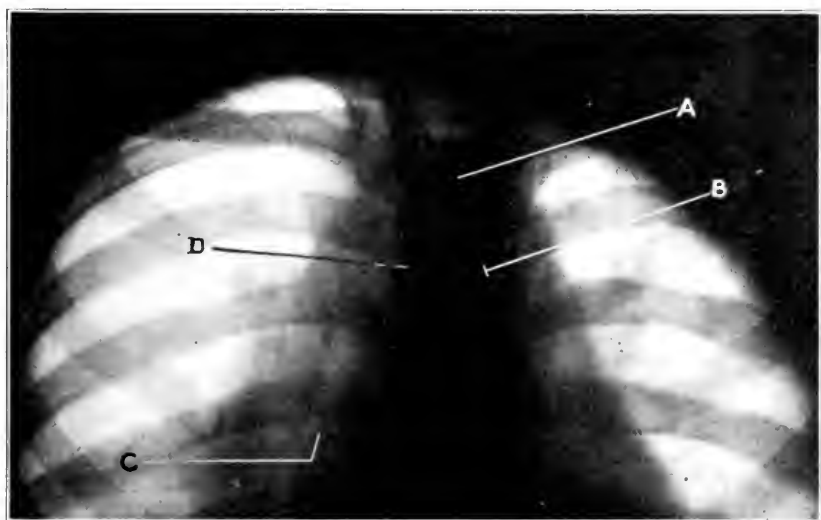


Fig. 5.—Roentgen ray of Helen A. (Case 1). Bifurcation trachea at *D*. Left border of trachea (*A*), left border of left bronchus (*B*). The extensive lesion at the right hilum is seen to the right of the heart whose right border is indicated by the inner end of line (*C*). Compare with physical signs and necropsy findings.

It should also be noted that the Roentgen ray did not reveal gland *C* (Fig. 4), as it lay behind the heart; hence a negative Roentgen-ray plate does not exclude glands along the left bronchus. She did not exhibit the inspiratory retraction ("hilum dimple") in the second and third interspace in the parasternal line which often is met with in children with peribronchial tuberculosis.

D'Espine's observations appear to have been made chiefly on infants and very young children. In older children and adults the bifurcation of the trachea is at a lower level than in the infant and for this reason the bronchophony is of questionable significance unless

heard down to or below the level of the fourth or fifth thoracic spine and its import is increased when heard at one or both sides of the vertebrae as well as over the spinous processes. It is very often present throughout the greater part of the interscapular space as is shown in Figure 2.

Its chief field of usefulness is in children in whom the tuberculous process is often limited to the tracheobronchial glands for months or years. It is also frequently of value in detecting peribronchial pathology in adults.

Several times this sign has been well marked in aged individuals with pulmonary tuberculosis in whom the usual signs were extremely indefinite.

As Hawes<sup>16</sup> 2d has recently expressed the opinion that this sign was of no value in this group it is perhaps worth while to refer to two of my cases that came to necropsy.



Fig. 6.—1, trachea; 2, left bronchus; 3, enlarged gland in angle between trachea and right bronchus.

The first was that of a woman of 66 who died of acute pericarditis and who had exhibited the D'Espine sign over the upper thoracic spine and slightly to the right. There was also some prolongation of the expiration at the right apex behind. At the necropsy no lesion of the apices was apparent but there was an enlarged gland just above the right bronchus (Fig. 6).

Another case was that of a woman of 64 whose history pointed to a tuberculous infection thirty years previously, during which time she had had occasionally slight activity. The signs of pulmonary involvement were indefinite, but the whispered bronchophony was always present throughout the interscapular space, being especially marked on the left.

16. Hawes 2d: *Am. Jour. Med. Sc.*, 1915, cxlix, 664.

At the necropsy marked enlargement of the bronchial glands was found especially those above and below the left bronchus (Fig. 7).

Another interesting case was that of a young man who for a time was thought to have typhoid fever because he had a high temperature, a low leukocyte count and a positive Widal. Throughout his sickness he exhibited a marked D'Espine's sign, especially to the left where it extended nearly to the lower angle of the scapula. The large mass of glands about the bronchi and trachea is shown in Figure 8.



Fig. 7.—Posterior view; part of left upper lobe removed. Large bronchial glands above and below left bronchus.

D'Espine's sign is best elicited when the arms are folded well across the chest, the head sharply flexed and the patient sitting erect. Firm pressure should be made with the stethoscope as the patient repeats "three thirty three." When the sign is positive the final "e" of the last word persists for a moment like an echo after the phonation ceases. This postphonal quality is the significant feature. Young children can often be made to repeat the word "tree" more easily than the usual phrase. Occasionally the spoken voice or cough brings out the echoing quality more than the whisper.

The following case illustrates the importance of investigating the hilum region after the method described by D'Espine.

A number of years ago it was decided that a young man had a tuberculous infection because of marked asthenia, a slight afternoon rise of temperature and a very positive von Pirquet tuberculin test.

He was examined within a few months by four specialists on tuberculosis of national repute, in different parts of the country. One detected a slight limitation of motion at the left apex together with a questionable dulness and a very few inconstant râles in the outer third of the left supraclavicular space.

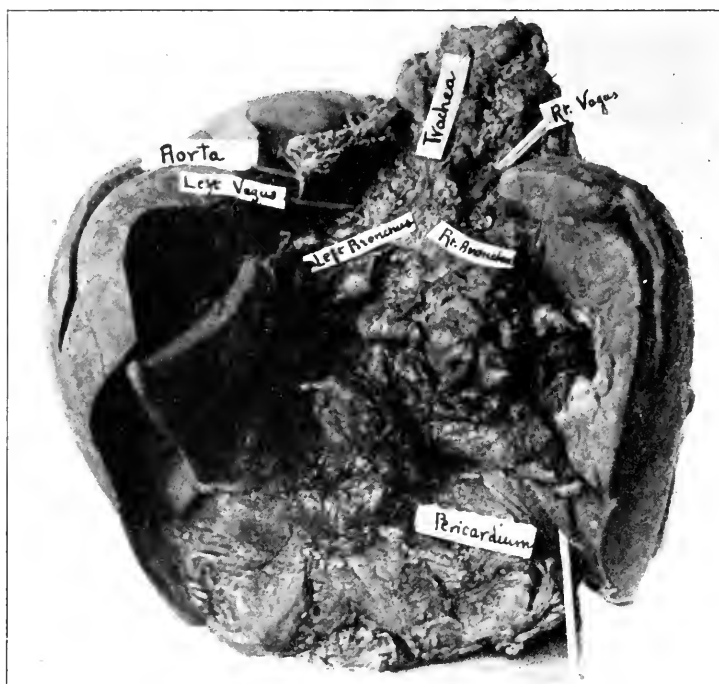


Fig. 8.—Posterior view made of lungs removed. Many glands above and below left bronchus, at the right root and along the right side of the trachea. Miliary tuberculosis of lungs.

A few months later the second expert found nothing but a few râles over the left lower lobe behind. Shortly thereafter a third specialist thought there was probably a healed lesion at the right apex though he did not believe the patient had any active tuberculosis. A few months later another man, the author of a well-known textbook on tuberculosis, found absolutely no trouble. As this was before the procedure described by D'Espine for detecting the presence of the enlarged bronchial glands, none of the men made a special study of the whispered voice in the hilum region posteriorly and no one expressed the opinion that the patient had peribronchial tuberculosis.

It was subsequently determined, however, that this patient had a very marked D'Espine sign, and roentgenograms demonstrated hilum disease and a few tubercles at both apices. The patient now presents bilateral retraction (hilum dimple) in the parasternal line of the third interspace.

#### SUMMARY

Whispered bronchophony in the interscapular space (D'Espine's sign) is indicative of a pathologic process at the hilum of the lung. This may be due to enlarged glands the result of malignancy, leukemia, Hodgkin's disease, syphilis or any infectious disease of the lungs. I have also seen it several times in aortic aneurism. Its presence in the delicate child is exceedingly suggestive of tuberculous involvement of the tracheobronchial glands.

Occasionally enlargement of the bronchial glands is present when there is no change in the whispered voice. In old people in whom the usual physical signs of pulmonary tuberculosis are sometimes exceedingly difficult to elicit the character of the whispered voice in the interscapular space should always be ascertained, as a well-marked D'Espine sign speaks for tuberculosis rather than for chronic bronchitis or emphysema.

The diagnosis of clinical tuberculosis, however, rests on the sum total of our physical signs and symptoms, not on one isolated sign.

I am indebted to Dr. Arthur J. Wolfe for the photographs of the patient in Case 1 (Figs. 2 and 3), which were taken in his laboratory.

75 Pratt Street.

# THE LONGITUDINAL SINUS AS THE PLACE OF PREFERENCE IN INFANCY FOR INTRAVENOUS ASPIRATIONS AND INJECTIONS, INCLUDING TRANSFUSION \*

HENRY F. HELMHOLZ, M.D.  
CHICAGO

The more frequently it has become necessary to obtain sufficient blood from infants for various diagnostic purposes in recent years, the more evident is the fact that the various methods of obtaining it are unsatisfactory. The method of scarification gives tissue juice in addition to blood and is not applicable for bacteriologic work on account of the frequent contaminations. The method of obtaining blood from the veins of the scalp, from the jugular or other veins, is very difficult and open to frequent failures. This is especially true in some toxic conditions in which even the external jugular is not to be seen or palpated.

From the anatomic point of view there is one place that is far superior to any other for the purpose of obtaining blood, namely, the longitudinal sinus in the area of the anterior fontanel. Inasmuch as the sinus grows gradually larger toward the back of the head, it is advisable to attempt the puncture as far posteriorly as possible. The course of the sinus does not vary and it is readily located from the external landmarks. The vein, furthermore, is rigid, cannot be pushed aside, and on entering the sinus one gets just as definite a sensation of being within the lumen of the vessel as one does in piercing the dura in making a lumbar puncture. When one takes into consideration the fact that punctures of the ventricles can be done without any harm, the damage that might result from an occasional puncture of the brain substance is negligible. This method offers a sure, easy way of obtaining blood from an infant under any and all circumstances.

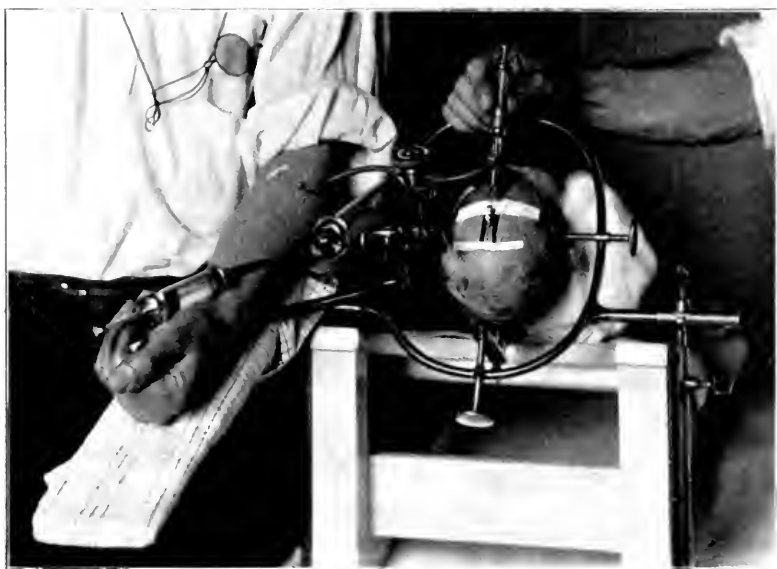
This does not exhaust the advantages of the sinus route. Just as readily as it lends itself to the obtaining of blood, can it be used for intravenous injection. Tobler<sup>1</sup> in a recent communication has pointed out the advantages of this method, which was first used by Marfan in 1898, for intravenous administration of salt solution. Tobler describes in detail the anatomy of the part and the technic of carrying out the puncture.

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\* From the Otho S. A. Sprague Memorial Institute Laboratory of the Children's Memorial Hospital.

1. Tobler, L.: Zur Technik der diagnostischen Blutentnahme und der intravenösen Injection beim Säugling, *Monatschr. f. Kinderh.*, 1915, xiii, 384.

My interest in the sinus puncture arose principally from the fact that it offered a solution of the difficulties of transfusion during infancy. Vein to vein anastomosis, by suture or tube, is a surgical procedure that requires an expert and special apparatus. The failure of the syringe method of transfusion is dependent, even in the hands of an expert, on the difficulty of getting into the infant's vein either directly or after cutting down on the vein. This is especially true of cases of melena of the new born in which the external jugular may be completely collapsed when dissected out. By using the sinus route this difficulty is completely obviated and the method becomes just as easy if not easier than a vein to vein syringe transfusion of the adult.



The figure illustrates the apparatus as it has been worked out for transfusion. Tobler's communication, coming at a time when only a few transfusions had been done, helped a great deal to give the author confidence in the method.

The question of negative pressure within the sinus is one that cannot be overlooked, and it is well always in entering the sinus to have a syringe attached, and always before injecting anything to withdraw blood, to make sure that the needle is in the sinus. To simplify this procedure without changing any connections, the needle that is to enter the sinus is attached to a two-way stopcock, which at one outlet is connected with a record syringe, and at the other with the transfusion apparatus. When the needle is inserted the stopcock is turned so as to connect with the record syringe, into which, as soon as the needle enters the sinus, blood is drawn. This blood can then be used for

bacteriologic examination or returned into the sinus. The valve is then turned and the blood is expelled from the needle with the saline solution which fills the transfusion apparatus. The apparatus used in transfusion is the one described by Unger.<sup>2</sup> The advantage of this method is that there is a constant flow in both directions when blood is drawn into the syringe from the donor, saline is going into the vein of the recipient, and when the blood is being delivered to the vein of the recipient, saline is going into the vein of the donor.

In order to steady the needle in the sinus I have used the little holder shown in the figure, which is fastened to the head with adhesive in such a way that the needle when pushed through the metallic guide will enter the most posterior portion of the anterior fontanel in the midline. The guide has several screw clamps so that when the needle has entered the sinus these can be tightened. The guide is set at an angle of 25 degrees with the scalp.

In the figure is shown the head holder that has been used in holding the infant's head in position. This is not absolutely necessary, but makes the transfusion much easier. For long continued injections of saline solution it is especially useful.

104 South Michigan Avenue.

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2. Unger, L. J.: A New Method of Syringe Transfusion, *Jour. Am. Med. Assn.*, 1915, *Ixiv*, 582.



## FURTHER STUDIES ON THE EPIDEMIC ABORTION REACTIONS IN CHILDREN \*

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AND

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MINNEAPOLIS

In a previous paper<sup>1</sup> we called attention to the fact that the blood serums of children consuming milk from cattle infected with contagious abortion often contain antibodies against *Bacillus abortus*.

Contagious abortion of cattle has been known to stockmen and dairymen the world over for the past century or more. There is probably no disease or combination of diseases which distresses the dairyman more or causes greater economic loss to him than this particular infection.

Up to the year 1896 the etiology of this disease remained obscure. In that year Dr. Bang<sup>2</sup> of Copenhagen isolated the organism which is now recognized as the specific etiologic agent in this disease. It is a short gram-negative, nonmotile bacillus which is somewhat difficult to isolate, but when once it has been grown successfully on artificial mediums its further cultivation presents few difficulties. The work of Bang shows that this bacillus is not only infectious for cattle, but for almost all of the domestic and laboratory animals. Ostertag found that it often caused abortion in mares.

In the domestic animals the site of infection appears to be in the uterine mucosa of pregnant animals. Until within the last two or three years the uterine mucosa was thought to be the only site of infection. Through the excellent work of Smith,<sup>3</sup> Fabyean,<sup>4</sup> Schroeder and Cotton<sup>5</sup> we know that the *Bacillus abortus* will affect laboratory animals and that abortion is not the only sign of infection. These authors have found that when a guinea-pig is inoculated intraperitoneally an infection occurs which cannot be differentiated macroscopically from tuberculosis. The spleen, especially, becomes very much enlarged and presents an appearance similar to that in an animal infected with tuberculosis. Not only the spleen and lymphatic system,

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\* Read before the Section on Diseases of Children at the Sixty-Sixth Annual Session of the American Medical Association, San Francisco, June, 1915.

1. Larson and Sedgwick: AM. JOUR. DIS. CHILD., 1913, vi, 326.

2. Bang: Ztschr. f. Tiermed., 1897.

3. Smith and Fabyean: Centralbl. f. Bakt. Referate, 1908, lxi, 549.

4. Fabyean: Jour. Med. Research, 1912, xxi, 441.

5. Schroeder and Cotton: Bull. Bureau of Animal Industry, 1912.

but the bones, liver, and kidneys have likewise been found to be extensively involved.

We have had opportunity in the last two or three years to go over the work of Smith, Fabyean, Schroeder and Cotton and can confirm the work of these authors in every particular. Laboratory animals that become infected do not always abort. In fact, we have had animals which showed the lesions above described in very pronounced degree carry to term. It thus appears that the type of lesion produced by the *Bacillus abortus* depends entirely on the animal infected.

Owing to the prevalence of this disease among cattle, it would be logical to expect to find that this organism is widely disseminated in market milk. From the excellent work of the Bureau of Animal Industry we know that a very large percentage of market milk contains this organism.

Before the work of the authors above referred to was made public, the question had raised itself with us as to the possibility of children who consumed milk from infected herds being infected. In our first series of 425 children whose blood was tested to either or both agglutination and complement-fixation reactions, we found that 17 per cent. of our cases gave a positive reaction. The further interesting fact was observed that children known to be supplied with milk from a perfectly clean herd, that is, one which had never been affected with contagious abortion, did not give this reaction, while those fed on milk purchased on the market gave a high percentage of positive reactions.

We were able to show by specific absorption tests that we were dealing with true antibodies against the *Bacillus abortus*, as a positive serum could readily be rendered negative by depleting it of its antibodies by absorption with the *Bacillus abortus*. The significance of these findings we were not able to determine; whether the presence of these antibodies is the result of an infection of the child or the result of antibody absorption through the digestive tract, cannot at present be definitely decided. While there is no positive proof that the reactions are due to an infection of the child, we are inclined to accept this interpretation. While it has been shown that antibodies are excreted in milk and that these may be absorbed through the intestinal canal, it would hardly seem probable that these antibodies could be excreted in the milk and absorbed by the child through the intestinal tract in sufficient quantities to give a positive complement-fixation and agglutination reaction. Bang has shown that animals may become infected by the intestinal tract just as readily and almost with the same degree of certainty as when the organisms are injected subcutaneously or intravenously. If the same is true of human beings, it will be readily seen how anyone who consumes milk is amply exposed to infection.

As we mentioned in our earlier contribution, we have found that women who abort do at times give a complement-fixation reaction when the *Bacillus abortus* is used as an antigen. In the bloods of aborting women examined by Larson this reaction was even more common than the Wassermann reaction. We are indebted also to Dr. A. W. Robertson of Litchfield, Minn., for the report of two women who aborted during the time that there was an epidemic of abortion among the cattle on their farms. In these cases he was able to find no other causes by which he could explain the expulsion of the fetuses. Although these reports are not yet sufficient to form a basis for definite conclusion, they are certainly suggestive.

Although our earlier 425 cases showed that 17 per cent. of the children gave a positive fixation and agglutination test for the *Bacillus abortus*, the children in some groups gave a much higher proportion, in fact over 40 per cent. of the children in one institution gave positive reactions and one group gave as high as 48 per cent.

It appeared to us that the next step in attacking this problem was the determination as to whether new-born children, who had as yet received no cow's milk, give this reaction. In a series of new-born children at the Minnesota University Hospitals the blood was collected from the cord at birth, or from the child's heel during the first few days after birth, and immediately examined. In all, 42 such new-born children were examined, without a single positive reaction. Eighteen of the above forty-two children were girls. Three of the above infants died and postmortem examinations showed:

1. Baby H.: Bronchopneumonia with cardiac dilatation.
2. Baby N.: Congenital syphilis and bronchopneumonia. This child gave a positive Wassermann and a negative abortus reaction.
3. Baby K.: Bronchopneumonia and congenital hydronephrosis.

Baby boy Cl., who was not included in the above series, as he received other feeding than breast milk, is exceptionally interesting. His blood gave a positive reaction using the *Bacillus abortus* as antigen. He was taken from the breast on the seventh day after birth as he had a high fever, the cause of which was not ascertained. He was then fed on artificial food containing cow's milk and on the twenty-first day the reaction was positive. This is the earliest positive bacillus abortion reaction which we have observed, and it is especially to be noted that the reaction was found two weeks after removal from the breast. The child recovered.

As an enlarged spleen is one of the findings that is observed in laboratory animals which have been infected with the *Bacillus abortus*, we were especially on the lookout for positive reaction in children with clinically demonstrable enlargement of this viscus.

Baby B. gave a positive reaction and had an enlarged spleen. It was 19 months old, with fair nutrition and had been on a general diet. The postmortem examination showed empyema, abscess of the lung, suppurative coxitis and adenitis.

Gladys K., who had an enlarged spleen, gave a complete inhibition. She was 10 years old and fairly well nourished. She was on a general diet. Her previous illness had been tonsillitis and pertussis. She was in the hospital for epilepsy, but gave at times very marked spasmophilic reactions.

Baby B., 2 months old, with pneumonia and an enlarged spleen, gave a negative reaction.

Ger, a girl 18 months old, with rickets and an enlarged spleen, also gave a negative reaction.

As this reaction is carried out in the same manner as the Wassermann test except that the *Bacillus abortus* is used as an antigen, the fact that the blood of five children with congenital syphilis gave negative reactions with this test should be recorded.

As bone lesions suggestive of rickets have been produced in laboratory animals by injection of the *Bacillus abortus*, the fact that several marked cases of rickets gave negative reactions is of interest.

Other conditions in which negative reactions were found were eczema, hydrocephalus, nephritis, atrophy, varicella, measles, diphtheria, bronchopneumonia, chorea, enteritis, anemia, imbecility and chronic pulmonary tuberculosis.

#### SUMMARY

1. This further study confirms our earlier report of the finding of a deviation of complement in children with the use of the *Bacillus abortus* as antigen.

2. New-born children who have been fed at the breast *only*, do not show the reaction. One baby, 3 weeks old, after having been off the breast two weeks and on a food containing cow's milk, gave a positive reaction.

3. The finding of positive reactions in children with large spleens is suggestive.

4. The blood of children giving positive Wassermann reactions may show no deviation of complement when the *Bacillus abortus* is used as antigen.

5. Children with many of the common diseases of children, including rickets, gave negative reactions. Much further study is, however, necessary with such conditions.

6. For the practicing physician, the importance of breast feeding and the desirability of the heating of all cow's milk administered is emphasized.

THE RESULTS OF VON PIRQUET REACTIONS  
MADE WITH OLD TUBERCULIN AND BOVINE TUBERCULIN ON THE  
CHILDREN OF THE STATE HOSPITAL FOR CRIPPLED AND DEFORMED  
CHILDREN AT ST. PAUL, TOGETHER WITH THE COMPLEMENT  
REACTIONS MADE ON THE BLOOD OF THE SAME CHILDREN  
WITH THE BACILLUS ABORTUS AS ANTIGEN

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There were in all 116 children examined, 58 boys and 58 girls. Von Pirquet reactions were made on all cases with old tuberculin and bovine tuberculin. Whenever a positive reaction was present for one, it was also present for the other. There were no exceptions to this rule.

Of the 58 boys, 20 reacted positive and 38 negative. Of the 58 girls, 22 reacted positive and 36 negative—a total of 42 positives and 74 negatives.

In 18 out of 20 positive reactions in boys, a clinical diagnosis of tuberculosis of the bone had been made. In the other two positive cases, one suffered from clubfoot and the other from infantile paralysis.

In 15 out of the 22 positive von Pirquet reactions in girls, the clinical diagnosis was tuberculosis of the bones or joints. Of the other 7 cases, one had clubfoot, 2 dislocated hips, 2 rickets, and 2 curvature of the spine.

Seventeen boys and 11 girls gave a negative von Pirquet when the clinical diagnosis was tuberculosis of the bone. Of the total number of 58 diagnosed clinically as tuberculosis, only 28 gave positive von Pirquet reactions.

COMPLEMENT-FIXATION REACTIONS WITH THE BACILLUS ABORTUS

Only 7 cases gave a positive complement reaction—6 boys and 1 girl.

*Diagnoses:* One ankle joint infection, von Pirquet negative.

One bow-legs, due to rickets, von Pirquet negative.

One tuberculosis of the hip joint, von Pirquet positive.

One tuberculosis of the hip, von Pirquet positive.

One old fracture of the tibia, von Pirquet negative.

One tuberculosis of the left hip, von Pirquet positive.

One curvature of the spine, von Pirquet negative.

All of the complement-fixation reactions were made by Dr. Larson of the Medical Department of the University of Minnesota, and most of the work in making the von Pirquets and in securing the blood was done by Dr. Giesler of the State Hospital for Crippled and Deformed Children.

## DOES THE BACILLUS ABORTUS (BANG) INFECT MAN? \*

MATTHIAS NICOLL, JR., M.D., AND JOSEPHINE S. PRATT  
NEW YORK

The frequent presence in milk of *Bacillus abortus*, the causative agent of contagious abortion of cattle and its pathogenicity for, or at least its ability to cause abortion in, many species of animals, raises the question whether it may not be infectious for man. Mohler and Traum<sup>1</sup> tested the serum of forty-two persons by the agglutination and complement-fixation reaction with negative results. Fifty-six adenoids and tonsils from milk-consuming children were injected into guinea-pigs. The material from one case produced nodular areas in the liver, but cultures remained sterile. The injection of tonsils from another patient produced typical lesions in guinea-pigs and *B. abortus* was isolated. More recently Larson and Sedgwick<sup>2</sup> presented further evidence of the possible infection of man. They found that some women giving a history of abortion gave a positive complement-fixation reaction using *B. abortus* as antigen. They also examined the blood of 425 children, and 73, or 17 per cent., gave positive reactions. These results were checked by the agglutination reaction, which gave parallel results. The positive reactions were among children having bone lesions, mostly diagnosed as tuberculosis and rickets. As they point out, inoculation of cultures into guinea-pigs produces bone lesions, which may be epiphyseal enlargements, as well as lesions of the lymphatic nodes, spleen, liver, kidney, testicle and lungs.

As noted, the *B. abortus* has been isolated only once from human tissues. As this was a tonsil, the bacillus may have come from the milk ingested and is of no value as evidence of infection. The presence of serum reactions are suggestive, but they again are not conclusive, failing the isolation of the bacillus from the lesions. That the ingestion of bacilli in large doses may be followed by the presence of antibodies in the blood has been demonstrated by several investigators. We have had similar results in feeding guinea-pigs with typhoid bacilli.

Because of these findings of Larson and Sedgwick, we have tested a large number of serums, using the agglutination reaction. This method was selected as simpler to carry out and because of the con-

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\* Submitted for publication June 27, 1915.

\* From the Division of Laboratories, Department of Health, New York.

1. Mohler and Traum: Bureau of Animal Industry, Circular 216, 1911.

2. Larson, W. P., and Sedgwick, J. P.: AM. JOUR. DIS. CHILD., 1913, vi, 326.

sensus of opinion that the agglutination reaction runs parallel with the complement-fixation reaction. Most of the cases have been infants or children who were inmates of a foundling asylum, and included cases of marasmus, rickets, enlarged lymph nodes, hypertrophied tonsils or adenoids, as well as about one hundred newly admitted infants from a few days to 2 months of age.

With few exceptions none of the serums from these infants had agglutinative power when tested in dilutions of 1:10 and 1:50. Two samples of serums from one child 3 years old, having bow legs and saber tibiae, undoubtedly rachitic, gave a good reaction as high as 1:100. The serums from two other children  $2\frac{1}{2}$  and 5 years old, respectively, with no noteworthy clinical abnormalities, gave slight reactions in the 1:10 dilution. The serum from another child, 3 years old, having enlarged tonsils and adenoids, gave a complete reaction at 1:200, the highest dilution tried. Swabs were taken from the tonsils of this child and the material injected into guinea-pigs. Later the tonsils were excised and after being ground up were also injected into guinea-pigs. These pigs developed no agglutinins for *B. abortus*, and were negative on necropsy, as were also cultures made from their organs. The serums from five other children with enlarged tonsils and adenoids gave a moderate or marked reaction in a dilution of 1:10 only. The tonsils were obtained but the guinea-pig inoculations were without result.

A case present in the obstetric ward of the above institution because of a seven months' miscarriage, but giving a negative Wassermann reaction, was investigated. The serum of the mother reacted up to 1:300, but became less active later, reacting only at 1:100 five months later. The serum of the child gave about the same reaction on one test. The foster-child of this woman was also tested with negative results. The vaginal discharge and milk from the mother and feces from the child were obtained and injected into guinea-pigs, with completely negative results.

The serums from twelve children having enlarged tonsils and adenoids were obtained at a dispensary. One gave a slight reaction at 1:10 dilution. The tonsils were ground up and injected into guinea-pigs without result. The serums from two other cases of miscarriage were also tested. In one case the only history obtained was of a seven months' miscarriage. The other patient had borne two dead children and more recently miscarried at four months. The Wassermann reaction was negative, but the patient was nephritic. Both serums gave no reaction even in low dilutions.



What interpretation one is justified in making from the above findings is doubtful. The serums from two children, one a child with enlarged tonsils, the other a case of miscarriage, gave unusually high reactions. Failing successful isolation of the *B. abortus*, such findings, as well as those reported by Larson, are only suggestive. We can at least say that no conclusive evidence has as yet been advanced that the *B. abortus* produces lesions in man.

# QUANTITATIVE DETERMINATIONS OF NONPROTEIN NITROGEN IN THE BLOOD OF THE NEW-BORN \*

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The nonprotein nitrogen fraction of the blood has for some time been the object of considerable study. This is due partly to the recognized intimate bearing it has on protein metabolism of the tissues, particularly the problem of the fate of protein digestion in the body, and partly due to the publication of methods which made possible a much more accurate determination of this fraction than was heretofore possible.

The studies and observations recorded so far are confined entirely to the blood of the human adult and of lower animals. To our knowledge, there is no reference in the literature on pediatrics to a study of the nonprotein fraction of nitrogen in the blood of the infant.

The quantitative determination of this fraction and some of its components in the newborn at various ages and at different periods of digestion, was the object of our study.

The difficulty in securing the blood from the living infant necessarily limited our observations to a study of the systemic blood only.

The total nitrogen, urea, ammonia and amino-acid nitrogen were determined quantitatively in a series of twenty-six infants varying in age from one half hour to 10 days old.

The source of the nonprotein nitrogen is almost entirely from the proteins ingested into the organism. There is considerable diversity of opinion as regards the fate of these protein digestive products in the body. Van Slyke and Meyer<sup>1</sup> have formulated the views held on this question at the present time under four hypotheses.

1. Ingested proteins are absorbed and incorporated into the body without undergoing any marked chemical change.

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\* Read before the Section on Diseases of Children at the Sixty-Sixth Annual Session of the American Medical Association, San Francisco, June, 1915.

\* From the Minneapolis City Hospital and the Department of Medicine, Division of Pediatrics, University of Minnesota.

1. Van Slyke, D., and Meyer, G.: Jour. Biol. Chem., 1913-14, xvi, 197.

2. Food proteins are first hydrolyzed in the alimentary tract. The products of digestive hydrolysis are absorbed into the blood and carried to the tissues.

3. The products are deaminized in the walls of the intestine before entering the circulation.

4. The products are synthetized into serum proteins before entering the circulation.

While some of these hypotheses have at least in part been sustained by experimental proof, the work of Folin and Van Slyke and their co-workers, working with newer and much more accurate methods, has shown that these hypotheses are probably all more or less incorrect. Their results seem to indicate that the ingested proteins are completely hydrolyzed in the digestive tract. Most of their amino-acids are thus set free. These are absorbed into the blood stream unchanged and from there are taken up by the tissues.

Recent investigations in this field have brought out many interesting facts and have changed some of the prevailing views on protein metabolism.

The figures published by various observers on the amount of total nonprotein nitrogen (by this is meant the nitrogen not precipitated by methyl alcohol and zinc chlorid, Folin's method) in normal adult human blood, vary within wide limits. Partly this is due to the method used.

Schöndorf,<sup>2</sup> Strauss,<sup>3</sup> Rowntree and Fitz,<sup>4</sup> Hohlweg,<sup>5</sup> Widal and Ronchese<sup>6</sup> and Agnew<sup>7</sup> report maximum figures ranging between 50 and 70 mg. per 100 c.c. of blood.

Farr and Austin<sup>8</sup> and McLean and Snelling<sup>9</sup> found much lower values.

Folin and Denis<sup>10</sup> report a maximum of 22 mg. per 100 c.c. of blood. They found the nonprotein nitrogen in the portal blood at any given time higher than in the systemic venous blood. Urea nitrogen in the blood forms the largest percentage of the nonprotein nitrogen found there.

Many of the authors before mentioned quote figures between 50 and 70 per cent. In this case again the older methods give much higher

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2. Schöndorf: *Pflüger's Arch.*, 1899, lxxix, 358.

3. Strauss: *Die Chr. Nierenentzündigen*, Berlin, 1902.

4. Rowntree and Fitz: *Arch. Int. Med.*, 1913, xi, 258.

5. Hohlweg: *Deutsch. Arch. f. klin. Med.*, 1911, civ, 216.

6. Widal and Ronchese: *Compt. rend. Soc. de biol.*, 1906, lx, 245.

7. Agnew: *Arch. Int. Med.*, 1914, xiii, 485.

8. Farr and Austin: *Jour. Exper. Med.*, 1913, xviii, 228.

9. McLean and Snelling: *Jour. Biol. Chem.*, 1914, xix, 36.

10. Folin and Denis: *Jour. Biol. Chem.*, 1913, xiv, 29.

results. Folin and Denis<sup>10</sup> found between 11 and 13 mg. per 100 c.c. in human adult blood.

Recent investigation has shown some interesting facts in regard to the urea formation and distribution in the animal organism. Folin and Denis<sup>11</sup> found that urea formation was a characteristic of all the tissues, the greatest amount probably being formed in muscle, and that contrary to older conceptions, there was no specific organ for its formation. Folin believes that the amino-acids are in the end the essential source of urea. Marshall and Davis<sup>12</sup> and Fiske and Sumner<sup>13</sup> confirmed the work of Folin and Denis. They showed by direct experiment that urea could be formed from amino-acids even if the liver was cut out of the circulation.

The introduction of newer and more accurate methods showed the ammonia nitrogen fraction of the blood to be much smaller under both normal and abnormal conditions.

Folin and Denis<sup>11</sup> found that the portal blood contained more ammonia nitrogen than the systemic blood and that the amount of ammonia in the systemic blood under ordinary normal conditions was infinitesimal in amount. They were able to show also that the greater amount of the ammonia in portal blood is derived from the large intestine.

Recent publications have dealt largely with the amino-acid nitrogen in the blood. It is the most important fraction of nonprotein nitrogen.

Delaunay<sup>14</sup> working with the formol titration method of Sørensen<sup>15</sup> first demonstrated the presence of amino-acids in the blood of animals. The amount varied in different parts of the circulatory system, but was generally low in the systemic and high in the portal circulation. Preceding him, Van Slyke<sup>16</sup> had devised a very accurate gasometric method for the determination of amino-acids in fluids and tissues.

Van Slyke and Meyer<sup>17</sup> found that the blood of the fasting animal contained from 3 to 5 mg. of amino-acid nitrogen; also that introduction of amino-acids into the small intestine increased the amino-acid nitrogen of the blood of the mesenteric vein from 3.9 to 6.3 mg. per 100 c.c., and this increase affected the blood from the femoral artery almost as much as that taken directly from the mesenteric vein.

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11. Folin and Denis: *Jour. Biol. Chem.*, 1912, xii, 141.

12. Marshall and Davis: *Jour. Biol. Chem.*, 1914, xviii, 53.

13. Fiske and Sumner: *Jour. Biol. Chem.*, 1914, xviii, 285.

14. Delaunay, H.: *Contrib. à l'étude du rôle des acides aminés dans l'organisme animal* Thèse de Bordeaux, 1910.

15. Sørensen: *Biochem. Ztschr.*, 1908, vii, 45.

16. Van Slyke: *Proc. Soc. Exper. Biol. and Med.*, 1909, xii, 46.

17. Van Slyke and Meyer: *Jour. Biol. Chem.*, 1912, xii, 399.

Abderhalden and Lampé,<sup>18</sup> using the ninhydrin color reaction, detected amino-acid nitrogen in the blood and confirmed the results of Van Slyke and Meyer.

Dobrowolskaja<sup>19</sup> found an increase in amino-acid nitrogen in both portal and peripheral systemic blood during digestion. Costantino<sup>20</sup> published similar results.

Wolkow<sup>21</sup> found only a slight increase in the peripheral blood, generally about 4 mg. to 100 c.c. of blood. The experiments of Van Slyke and Meyer proved conclusively that amino-acids normally pass the intestinal wall unchanged and enter the blood-stream directly, thus controverting a theory advanced by Abderhalden<sup>22</sup> that they are synthesized into blood proteins while passing the intestinal wall and are only broken down again to amino-acids when they reach the tissues.

In the series of cases we are reporting all the determinations are only on systemic venous blood. From 15 to 20 c.c. of the blood were taken under aseptic precautions from the median basilic vein of the arm and at once taken to the laboratory for the determinations.

In four of the cases the infants had not yet been fed; in one of these cases the blood was taken one-half hour after birth. In the other cases the period after feeding at which the blood was taken varied between one-half and four hours.

The ammonia determinations were generally completed within less than one hour after taking the blood.

Total nitrogen, urea and ammonia were determined according to the micromethods devised by Folin and Denis.<sup>23</sup> In a part of the series, the urease method recently published by Van Slyke and Cullen<sup>24</sup> was used. The amino-acid nitrogen was determined according to the gasometric method of Van Slyke and Meyer.<sup>25</sup> Five cubic centimeters of blood were used for all the individual determinations except those done with the urease method. In these 3 c.c. of blood were used. A few of the amino-acid determinations were carried out on 2 c.c. of blood (Cases 1 and 2). The urea and total nitrogen were determined together in the same specimen of 5 c.c. In this determination the blood was precipitated with methyl alcohol and the filtrate again with zinc chlorid. The slight modification recommended by Bock and Benedict<sup>26</sup> of distilling off the ammonia instead of driving it over with

18. Abderhalden and Lampé: *Ztschr. f. physiol. Chem.*, 1912, lxxxi, 473.

19. Dobrowolskaja: *Ztschr. f. physiol. Chem.*, 1913, lxxxvii, 325.

20. Costantino: *Biochem. Ztschr.*, 1913, lv, 402.

21. Wolkow: *Ztschr. f. physiol. Chem.*, 1913, lxxxvii, 334.

22. Abderhalden: *Synthese der Zellbausteine*, 1912.

23. Folin and Denis: *Jour. Biol. Chem.*, 1912, xi, 527.

24. Van Slyke and Cullen: *Jour. Biol. Chem.*, 1914, xix, 211.

25. Van Slyke and Meyer: *Jour. Biol. Chem.*, 1912, xii, 402.

26. Bock and Benedict: *Jour. Biol. Chem.*, 1915, xx, 41.

TABLE SHOWING NONPROTEIN NITROGEN DETERMINATIONS

Case Number	Infant's Weight gm.	Age of Child	Hours After Feeding	Total Non-Protein Nitrogen	Urea Nitrogen, Folin-Denis	Urea Nitrogen, Van Slyke	Urea Nitrogen, Per Cent.	Ammonia Nitrogen	Amino-Acid Nitrogen, Van Slyke
1	3,120	2 days	3	.....	.....	.....	....	.....	0.001
2	2,980	4 days	4	.....	.....	.....	....	.....	0.001
3	2,850	5 days	4	0.023	0.014	.....	60.8	0.0005	0.0004
4	3,000	3 days	2	0.044	0.014	.....	31.8	0.0006	0.002
5	2,945	2 days	3½	0.032	0.012	.....	37.5	.....	0.006
6	2,580	8 days	2	0.024	0.008	.....	33.3	.....	.....
7	2,165	10 days	2½	0.023	0.015	.....	43.4	.....	0.005
8	3,200	2 days	1½	0.037	0.024	.....	64.8	0.0004	0.003
9	3,550	9 days	½	.....	.....	.....	....	.....	0.003
10	2,800	2 days	½	.....	.....	.....	....	.....	0.003
11	3,280	12 hours	1½	0.032	0.018	.....	56.2	0.0003	0.005
12	2,860	2 days	4	.....	.....	.....	....	0.0003	0.003
13	3,395	9 hours	Not fed	.....	.....	.....	....	.....	0.005
14	3,325	4 days	3	.....	.....	.....	....	.....	.....
15	2,650	8 days	3	.....	.....	.....	....	0.0003	0.005
16	2,640	8 hours	Not fed	0.040	0.016	.....	41.5	0.0003	0.003
17	3,690	8 days	3½	.....	.....	.....	....	0.0002	.....
18	3,450	3 days	4	.....	0.020	0.021	....	0.0003	0.0003
19	3,620	13 hours	3	.....	.....	0.016	....	0.0002	.....
20	3,225	1 hour	Not fed	.....	.....	0.006	....	0.0002	0.002
21	3,760	½ hour	Not fed	0.023	.....	0.004	17.3	0.0002	0.003
22	3,800	2 days	½	.....	.....	0.015	....	0.0002	0.001
23	3,350	6 days	1	.....	.....	0.005	....	.....	.....
24	3,715	12 days	1	.....	.....	0.006	....	0.0004	.....
25	3,400	8 days	3½	.....	.....	0.013	....	0.0003	.....
26	3,900	20 hours	4	.....	.....	0.009	....	0.0003	0.002

an air current was used in both total nitrogen and urea determinations. In the urea determinations with the urease method, ammonia and urea are combined.

Van Slyke found the ammonia fraction so small, if the blood is used within one hour, that it can be disregarded. The urea determinations with Folin's method and the urease method of Van Slyke check closely. In the amino-acid determinations the blood was precipitated with ethyl alcohol and allowed to stand for twenty-four hours. A review of our different results shows that the total nonprotein nitrogen per 100 c.c. of infant's systemic blood is approximately the same as in the adult. The age and weight of the infant and the period after feeding have no bearing.

The percentage of urea nitrogen is uniformly high and averages about 50 per cent. of the total nitrogen. It was lowest in the new-born infant one-half hour old, and in the infants which had not been fed.

The amount of ammonia nitrogen is extremely small in every instance and is also not influenced by the age of the infant or time after feeding. Probably the most interesting fact brought out is that amino-acids are constantly present in appreciable amounts in the infant's blood and were found present shortly after birth when no feeding had as yet been given. In this connection the work of Koelker and Slemmons<sup>27</sup> is interesting, possibly explaining the probable source of the amino-acid in the blood of the infant just born or before the first feeding. These authors isolated twelve different amino-acids from placental blood.

In the case of amino-acids again, the time of feeding apparently has no appreciable effect on the amount of amino-acids present in the systemic blood of the infant.

It can hardly be said that the changes in the nonprotein nitrogen in the systemic blood reflect the stages of protein digestion. It should be borne in mind that in this series no attempt was made to correlate the amount of food taken with the amounts of the various factors determined.

Further experiments bearing on this particular problem and also on the nonprotein nitrogen content of placental blood, are in progress.

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27. Koelker and Stemmons: *Jour. Biol. Chem.*, 1911, ix, 471.

# PROGRESS IN PEDIATRICS

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## RECENT PROGRESS IN INFANT WELFARE WORK \*

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During the past year, in spite of unfavorable conditions, financial and political, infant welfare work has steadily increased in extent and efficiency. Even from war-cursed Europe a few reports of progress have been received.

### PUBLIC ACTIVITIES

The federal Children's Bureau has been very active in investigating various phases of infant welfare work. Two most excellent studies in the field of infant mortality have been made in Johnstown, Pa.,<sup>1</sup> and Montclair, N. J.<sup>2</sup> Carefully collected data concerning the relation of sanitation, housing conditions, literacy, race, employment of women, attendance at confinement, method of feeding, etc., to infant mortality are well presented. While the localities studied are small, and the tabulations are based on too few cases to be conclusive when taken alone, when all these studies are completed they will form a most valuable addition to our knowledge of these subjects.

The Bureau has sent out to health officers of cities of 10,000 population and over and private organizations a carefully prepared list of questions concerning their activities, and when the answers have been compiled they will give most valuable information for those interested in this subject. The author was freely permitted to study these reports and much of the information given below was obtained therefrom.

During the past year the Kansas State Department of Health has organized a division of child hygiene, so that New York is no longer the only state with such a division. Steps are being taken toward the organization of a similar division in Ohio, and Louisiana and Massachusetts have well defined branches of the State departments of health giving attention to the subject. The majority of the states are now more or less actively engaged in infant welfare work. At least sixteen have exhibits on the subject. Louisiana and Texas have fitted up exhibit cars which travel all over the state. In twenty-two lectures

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\* Submitted for publication July 6, 1915.

1. Infant Mortality. Results of a Field Study in Johnstown, Pa., Based on Births in One Calendar Year. Bureau Publication No. 9, Washington, 1915.

2. Infant Mortality. Montclair, N. J. A Study of Infant Mortality in a Suburban Community. Bureau Publication No. 11. Washington, 1915.



are given as part of the regular activities of the department. Twenty-three states issue special bulletins or booklets on the care of the baby, which are widely distributed, in some cases one being sent to the mother of every baby whose birth is registered. The public press is used in spreading information by fourteen states.<sup>3</sup>

Probably the most extensive campaign carried on was in New York. As a preliminary a letter was sent out by the Commissioner of Health to all health officers in the state asking for their cooperation, and for information as to the needs in their particular localities. The objects of the campaign were, "to educate the mother in the care and feeding of her child, to arouse the community to the necessity for child welfare work, to point out the fact that a high infant mortality was unnecessary and should be considered a disgrace, to establish infant welfare centers with the employment of nurses, and to improve the general milk supply." Three special exhibits were prepared and those of the Rochester department of health and the Russell Sage Foundation were borrowed. During April, May and June these exhibits were shown in forty-five cities and large villages, over 150 public meetings had been held in connection with them and over 79,000 people had been reached. Three additional exhibits were prepared dealing especially with rural hygiene and, with the other exhibits, were shown during August and September at fifty-five county fairs, the State Fair, and the Rochester Industrial Exhibition. Ten requests for them had to be refused.

All exhibits were in charge of a trained nurse or specially trained person. Advice and literature were given, and, in addition, special meetings were held for mothers and prospective mothers. The older girls in the public and parochial schools were given talks and demonstrations, and, when requested, the nurse did a certain amount of home instructive visiting. In certain places two moving picture films were used in connection with the exhibit, on the care of the baby and on the subject of pure milk.

Wherever the exhibits were shown an attempt was made to arouse public interest and to try to secure the establishment of infant welfare stations. In 1913 there were thirty-two such stations in twelve localities outside of New York City. As a result of this campaign, by the end of 1914 there were sixty-seven stations already established in thirty-two different localities.

This was only a part of the activities of the department. Among others may be mentioned a campaign to establish a state organization of "Little Mothers' League," sending its pamphlet "How to Save the Babies" to the mother of every baby whose birth was registered, with

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3. Information obtained from the Children's Bureau.

a letter from the commissioner, and within the last few weeks the organization of a State-wide Baby Welfare Sunday.

How much good is accomplished by the distribution of literature is still something of an open question. That it does have some effect and is appreciated is shown from the following letters.

Locust Valley, N. Y., Dec. 21, 1914.

New York State Department of Health, Albany, N. Y.

*Gentlemen:*—A few days ago my wife received from you the "Baby Book." We cannot begin to express our gratitude to you for this little book. It is a Godsend to any mother with a little baby. It is being the means of saving thousands of lives and untold hours of care and worry.

I have two sisters. One has a baby several months old, and the other will be a mother this coming spring. If it is not asking too much, I would like two more baby books—one for each of these women.

Thanking you again, I remain

Yours very truly,

Yonkers, N. Y., Dec. 5, 1914.

*Dear Sir:*—Recently one of my young mothers received a pamphlet from you, the title of which, I believe, was "Your Baby—How to Keep It Well." I would like to ask if each mother is to get one? I was much pleased with the pamphlet and would like one myself.

Yours sincerely,

Dr. \_\_\_\_\_

P. S. It seems to me that if the doctors, nurses and midwives were included in the distribution of the pamphlet it would be of value.

The report of the Division of Child Hygiene of the New York State Department of Health will soon be published, and is worth careful study. The infant mortality rate in the state, outside of New York City, fell from 125 in 1913 to 111 in 1914.

The activities of city departments of health have also increased very much in scope. Ninety-nine state that they are doing instructive work among mothers through visiting nurses; thirty-seven that they are maintaining welfare stations; and thirty-eight that they are doing pre-natal work.

#### INFANT WELFARE STATIONS

A year ago I was able to report the existence of 204 such welfare stations in thirty-nine cities and towns. The Federal Children's Bureau this year have secured data concerning 462, of which 290 are maintained by private organizations in ninety-two cities.<sup>3</sup>

A very interesting bit of evidence as to the value of these welfare stations is contained in a communication from Miss Jean Halford, secretary of the British National Association for the Prevention of Infant Mortality. She says:

The war has helped to arouse the conscience of the nation, as perhaps nothing else would have aroused it, to a sense of the supreme importance and value of healthy motherhood and infancy, with the result that more new infant wel-

fare centers have been established since the outbreak of hostilities than ever before in so short a time. Much of this development has, however, been due to the work of eight organizers appointed by the Association of Infant Consultations and Schools for Mothers. . . . So great was the enthusiasm aroused in this way that new centers were formed and are still being formed at the rate of four or five every week, sometimes holding the first infant consultation within a fortnight of the visit of an organizer. The consequence is that during the first eight months of the war over 100 new schools for mothers, many of which included dining rooms for nursing and expectant mothers, were actually started, while some 200 more will shortly be ready to open. . . . So far only towns with a population of 20,000 or more have been tackled.

The English government now grants to these stations funds from the public treasury up to 50 per cent. of the approved expenses. This in spite of the tremendous drain on the financial resources of the Empire.

The effort is being made in several places in this country, notably New York, Philadelphia, and, more recently, Buffalo, to develop the infant welfare station to its highest degree of efficiency. In New York this work is being carried on by the New York Milk Committee and is the development of the experiments and demonstrations of the value, first, of the milk station in reducing infant mortality—especially that due to diarrheal disease—and, later, of the mortality due to stillbirths, congenital debility, prematurity, etc. The work is being done in one of the most neglected and insanitary districts in the city and the effort is being made to make the "Health Center" the central point for all the health protective activities in this district. The safeguarding of the public health, whether of babies or adults, after the first broad general principles have been established, must be in large part a local matter. This is especially true in our large cities, notably those near the coast. Where many nationalities are represented there is a tendency for them to segregate and the problems arising differ very materially for these different groups of people. At the Health Center the effort is made to get in touch with every family in the district in which the center is located and to make it the natural headquarters for all matters pertaining to the health and welfare of the entire family, especial effort and attention being given to the children. Infant consultations are held every afternoon; the nurses make home visits of instruction and supervision; thorough prenatal instruction is given, and the nurse acts as advisor and friend in all questions directly or remotely connected with the health of the family. The most complete and cordial cooperation exists between the Health Center and the various city departments having charge of street cleaning, tenement houses, fire protection, police and health administration, as well as all other organizations in any way doing any form of work for the betterment of living conditions in this district. This work was started nearly two years ago and since that time has been taken up

along very similar lines in Philadelphia and, within the last few months, also in Buffalo.

#### REDUCTION OF INFANT MORTALITY DURING THE FIRST WEEKS OF LIFE

No form of infant welfare work has appealed so strongly as that directed toward saving the lives of babies by trying to secure to them a fair start in life. It is very difficult to estimate the results of this work at present, owing to differences in methods employed, and the varying ways of tabulating statistics. It is also possible that several of the organizations claiming to be doing prenatal work are doing it in a very casual and haphazard way. So far as is known, however, thirty-eight city health departments and 247 private agencies are doing this kind of work in 110 different localities.<sup>3</sup> In St. Louis, the Children's Hospital and the obstetric department of Washington University are carrying out a well organized work for babies, beginning from the day the mother reports to the obstetrics clinic and continuing until the baby is 1 year old. A report on their prenatal work has already been published. A further report is in preparation, dealing with the results of their work through the first year of the baby's life.

In New York City, the Department of Health has carried on this work in connection with its milk stations. An attempt has been made for two years to secure special funds from the city to provide an adequate nursing force to do intensive work along these lines, but, owing to the financial situation, it was unable to obtain them. During the year 1914, 1,622 mothers were registered. Of these 898 women had been confined and at the end of the year 409 were still under observation. There were 900 births among these 898 women, with a still-birth rate of 34.4 per 1,000 births and a death rate among the babies under 1 month of age, based on living births, of 19.5 per 1,000. Over 90 per cent. of the babies living at the end of the first year were being breast fed.

#### INSTITUTIONAL MORTALITY, THE ILLEGITIMATE BABY

During the past year increasing attention has been given to the problem of the mortality among so-called foundling institutions. Receiving, as they do, great numbers of illegitimate babies, whose start in life is always an unfavorable one, the mortality in these institutions has been known for years to be high. Unfortunately it has been regarded as more or less inevitable and little attention has been paid to the subject. The American Association for Study and Prevention of Infant Mortality, through their Committees on Pediatrics and Social and Vital Statistics, undertook a preliminary study of this subject. Every child admitted to the three large institutions in New

York City receiving foundlings, abandoned or neglected babies, was traced through its first year, or up to the time of its death during its first year. The report of this committee<sup>4</sup> contains some startling facts. It was found that of 1,738 babies, 51.61 per cent. died under 1 year of age. Most of them were admitted to the institutions without their mothers and no less than 50.1 per cent. were deliberately abandoned by their mothers at the institutions. Of those whose mothers remained with them and nursed them for a time at least, the mortality was only 27.11 per cent. as against a mortality of 51.61 per cent. for all the babies admitted. It was found that 22 per cent. died within less than one month, and nearly 35 per cent. in less than two months after admission. While this would seem to bear out the claim so often made that the death rate is high on account of the bad physical condition of the baby, the fact that of 209 babies who were born in the institution and whose mothers had been under careful supervision for several months before the birth of the baby, only 7 per cent. died during their first month and 20 per cent. in less than two months, yet before the first year was over 48 per cent. had died, suggests forcibly the need of more careful study of the problem of the effect of institutional environment.

The New York City Department of Charities has already undertaken an investigation of the institutions caring for its youthful charges and has found that the conditions existing in many of them are medieval. These conditions were summarized in a recent paper by the Second Deputy Commissioner.<sup>5</sup>

An effort has been made in New York City, through cooperation between the New York Foundling Hospital, the City Department of Health and the Russell Sage Foundation, to reduce the mortality among "marasmus babies" in these institutions. It is generally admitted by those familiar with the subject that from 75 to 100 per cent. of these babies in institutions die. In this investigation marasmus babies were placed out with foster mothers specially selected for their intelligence, and a bonus of five dollars a month was given to them for special care. They were under constant supervision of the nurses and inspectors of the Department of Health, were required to be taken regularly to the nearest welfare station, and everything was done to insure their having the best chance possible. It is stated that the "results of this experiment have been most encouraging, not only as far as life saving is concerned, but particularly with regard to the restoration to complete health of the babies cared for. Up to the

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4. Mortality in So-Called Foundling Institutions. Trans. Fifth Ann. Meeting Am. Assn. for Study and Prev. Infant Mortality, Baltimore, 1914.

5. A Study of Results of Institutional Care. Hon William J. Doherty, National Conference Charities and Correction, Baltimore, 1915.

present time, the reduction in the death rate among these infants has been about 50 per cent.”<sup>6</sup>

In Europe the problem of the illegitimate baby has become a very acute one. Belgium and portions of France which have been overrun by invading armies have one phase in its most distressing form, while all the countries of Europe where enormous armies are gathered have another phase to consider. In France the subject of the “war baby” has been squarely met by the authorities. It is said:

. . . The object of these emergency measures is not only to avert unnecessary suffering from the victims of brutality and license, but to save the lives of the children about to be born by removing the temptation to infanticide. To this end the customary formalities and inquiries so dear to the official mind—so particularly dear to the French official mind—are for the time being relaxed and practically waived; in place of the usual precautions and deterrents every effort is to be made to induce the woman who has been a victim of war at its foulest to claim the protection of the state for herself and her unborn child.

Hence it has been enacted that in any commune which has been occupied by German troops the simple certificate of a doctor—sent straight to the local prefect and not handled by subordinate officials—will give the woman to whose condition the doctor has testified a claim on public assistance and entitle her to a gratuitous treatment and the payment of necessary expenses. Further, should any woman prefer to conceal her misfortune, not only from her neighbors, but from the local doctor and the local prefect, a maternity hospital in Paris will be open to her without any other credential or formality than the proof of her residence in a part of the country which has been occupied by the German army.

The mother, of course, is only half the problem; when you have made provision for her in her hour of need, provision for the actual birth of her child, there still remains the question of the fate of the child so born. Here, again, the state has flung its caution and precaution to the winds and assumed the full responsibility, and by so doing has recognized the right of the woman to be relieved of a burden forced on her. Unless it is otherwise desired by the mother, the child from the day of its birth will be treated as an orphan and a foundling; whatever its birthplace, it will be sent to Paris and duly registered, not in the archives of the commune in which it was born, but from the Paris institution in which it will be tended and reared. By this means its identity will be concealed, all traces of its origin lost, and the knowledge of its parentage hidden from itself as well as from the outside world; it will grow up among other fatherless and motherless children, unconscious of the sin that gave it life and of the alien blood which would be an added stain on its birth.

In England, which has not been overrun by the invaders, but which has been turned into a great training camp, the problem is different, but it is no less of a problem. Committees have been formed to investigate the extent of illegitimacy, and the matter has been taken up in the House of Commons.

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6. Personal letter from Dr. S. Josephine Baker, Chief Division of Child Hygiene, New York City Department of Health.

## PREVENTION OF DIARRHEAL DISEASE

*Fly Prevention.*—During the last few years, the common house fly has come in for considerable attention as to its relation to diarrheal disease among babies. An extensive study has been carried out by the New York Association for Improving the Condition of the Poor with the assistance of the health department. Preliminary reports on their work have already been presented and the detailed report is about to go to the press. The investigation was carried out under the most carefully considered conditions and with very thorough supervision. The results obtained are, to say the least, very suggestive. In a certain locality in the city, after a careful census of the families living in tenement conditions, half were selected to receive all advice, supervision and care which could be given, except vigorous measures to protect from flies. The other half, in addition to the same general measures, agreed to follow out instructions looking directly to the protection of the child and its food from exposure to flies. The results of this, as shown by the prevalence of diarrheal disease in the two groups, is interesting. Nearly twice as many babies suffered from diarrhea during the period of the experiment among the unprotected group as among the protected. This was true to a less degree when the other phases concerned were considered, such as general cleanliness in the home, type of feeding, intelligence of the mother, etc.

In Richmond, Virginia, for the last two years, the Chief Health Officer, Dr. Levy, has instructed his infant welfare nurses to lay particular stress in their home visits on the necessity of immediate care of the stools of babies so that the risk of contamination of food, etc., by means of flies may be reduced to the minimum. Dr. Levy is convinced that this plan, carefully carried out, has had a great deal to do with the marked reduction of the diarrheal mortality in Richmond during the past two years.

## EFFORTS AT CO-OPERATION

The necessity for cooperation among all agencies working toward the saving of child life is becoming more and more appreciated every day. In Philadelphia a baby welfare association, working along the general lines adopted by an older organization in New York, has been formed. In both places the association acts as a clearing house for information and has an agency to secure prompt action in emergency. The motto of the New York organization, "To Save Babies by Saving Wasted Effort," explains its purpose. As an example of how such organizations can work may be mentioned one or two examples. In milk station work the great difficulty encountered by all has been to secure the attendance of mothers with their babies within the first

month after the birth of the baby. By an arrangement which has been perfected in New York, as soon as a mother and baby are discharged from a maternity hospital, the name and address and date of discharge are forwarded to the Babies' Welfare Association, which communicates with the nearest milk station, referring the child to it, and the mother is then visited by the nurse from the station and urged to enroll. During one month over three hundred cases were so referred by the maternity hospital.

In the promotion of breast feeding for babies, the association has made an arrangement whereby as soon as the death of a baby under 9 months is reported to the health department, the name of the mother is immediately sent to the association for investigation and the mother is asked whether she would be willing to wetnurse a baby in her own home or to go out as a wetnurse. By placing this information in the hands of institutions and physicians, it is hoped that much of the almost criminal separation of the wetnurse from her own baby and the unnecessary waste of wet nursing material may be prevented.

As a further evidence of the cooperation which is gradually springing up, in eight cities it is known that health departments and private organizations are jointly maintaining instructive visiting nursing, milk stations and prenatal work.

#### GENERAL EDUCATIONAL EFFORTS

The need of teaching girls in the upper grades of public schools the principles of personal hygiene and the elements of baby care, is every day becoming more clearly appreciated. For a number of years in England, the Board of Education has urged local authorities to include courses covering these subjects and has made detailed recommendations as to the way such instructions should be given. More and more in England are the public schools adopting the plan. In one school this course covers three years and includes all that is implied in "home making." A part of it includes practical instruction in bathing, dressing, and the general care of a baby, kind of clothing it needs, care of the bottles and the dangers of various superstitions and customs. In another school, in the last year the older girls are attached to home-making centers. Half of each day is devoted to practical work in home making. During several weeks the school room is converted into a nursery and they are taught how to look after children. In another school in London, part of the instruction consists of six weeks of practical work in a day nursery, under special instruction and supervision.

In Cleveland, during 1911 and 1912, the Babies' Dispensary demonstrated the feasibility and importance of teaching infant hygiene to the



girls of the public schools there. As a result, such teaching has gradually been incorporated into the regular curriculum of the schools so that, this year, every girl in a public school will get this course as part of her compulsory work before she graduates.

As has already been mentioned, the Department of Health in New York State, in cooperation with the Department of Education, is carrying on an extensive campaign for the formation of "Little Mothers' Leagues" in the public schools throughout the state.

During the summer of 1914 a very extensive campaign of education was carried out in New York City through holding a "Baby Week." The mayor of the city issued the call. Practically every organization in the city was called upon to take part in carrying out the program and all responded willingly. A letter was sent by the mayor, which was read in many of the churches and synagogues throughout the city. A similar letter was read to the children of every public school on the Monday of "Baby Week," followed by appropriate ceremonies in many of the schools. The rest of the week was given up to demonstrating the needs of the babies of the city and the work that was being done to meet those needs. The milk stations, day nurseries, hospitals, outing associations and other activities all came in for their share of attention. During the week the final baby contest was held, at which was selected the prize baby of the city. Previous contests had been held during the winter and spring and the winners of all these preliminary contests competed. The final ceremony was a parade of milk station babies with their mothers in Fifth Avenue motor busses, private automobiles and taxicabs, all of which were donated for the occasion, which parade was reviewed by the mayor, commissioner of health and other city officials and the prize baby and the winners of other prizes were presented by the mayor with their diplomas, after which the children and their mothers were given a ride through the park. There was a tremendous response from every side to this plan for stimulating interest. Department stores held special baby week sales. The newspapers gave much space to a description of the proceedings. The advertising companies donated space on their bill boards. The results of such a campaign is hard to judge, but from the requests for information received from all over the country, it may be said that "Baby Week" was a success in calling attention to the needs of the baby. Similar work has been carried on since in a number of other places and during the first week of July, a local "Baby Week" is to be celebrated in the Borough of Richmond, New York.

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## A CHEMICAL STUDY OF WOMAN'S MILK, ESPECIALLY ITS INORGANIC CONSTITUENTS \*

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No extended review of the literature on the chemistry of woman's milk will be attempted in this paper. The reader is referred for this to a résumé by Nothmann<sup>1</sup> in 1912 and another by Talbot<sup>2</sup> in 1914. Quite large series of analyses have been made by many observers in which only a determination of the organic constituents and the total ash of milk was aimed at. Among the most important publications are those of Leeds,<sup>3</sup> Meigs<sup>4</sup> and Adriance<sup>5</sup> in this country and those of Pfeiffer<sup>6</sup> and Schlossman<sup>7</sup> in Germany.

The fat and protein content of woman's milk are now pretty definitely agreed on. The methods followed by many chemists in the sugar determination, as we shall see later, are open to criticism; and even in the total ash estimation, errors have been made owing to faulty methods.

Considering how much work has been done on the chemistry of woman's milk, it is surprising that so few investigators have concerned themselves with the composition of the ash. With the exception of Harrington and Kinnicutt<sup>8</sup> who analyzed a single large composite sample, almost nothing has been published in this country and very little abroad on this subject. It is true that both here and abroad isolated analyses have been reported, but they have been mainly in connection with metabolism experiments and have frequently been

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\* Read at the meeting of the American Pediatric Society, Lakewood, N. J., May 26, 1915.

1. Nothmann: *Jahrb. f. Kinderh.*, 1912, lxxv, 724.

2. Talbot: *AM. JOUR. DIS. CHILD.*, 1914, vii, 445.

3. Leeds: Reprint, *Proc. Am. Assn. Adv. Sc.*, 1884.

4. Meigs: *Milk Analysis and Infant Feeding*, Phila., 1885.

5. Adriance: *Arch. Pediat.*, 1897, xiv, 22, 85.

6. Pfeiffer: *Verhandl. d. Versamml. d. Ges. f. Kinderh.*, Wien., 1894, p. 126.

7. Schlossmann: *Arch. f. Kinderh.*, 1900, xxx, 288.

8. Harrington and Kinnicutt: *Rotch, Pediatrics*, 1906.

made when the conditions were presumably pathologic. Even the writers who have undertaken to study the normal composition of the ash in woman's milk and who have been most extensively quoted in literature have made a surprisingly small number of observations.

The earliest modern investigator was Bunge<sup>9</sup> who published in 1874. Though his methods were exact, practically those in use today, so that his results can be relied on, yet his figures which have been so widely quoted were derived from two examinations of the milk of the same woman, one made on the fifteenth and the other on the eighteenth day of lactation. He used large samples, but he does not state that it was the twenty-four hours' secretion. Söldner,<sup>10</sup> whose work is also much quoted, published but six analyses, three of these being of colostrum and none being of milk at a later period than three and a half months. In only one instance was his examination of an individual sample. Pelka's<sup>11</sup> observations were but two in number, both made on composite samples. The single observations by Blauberg,<sup>12</sup> Abderhalden,<sup>13</sup> Birk<sup>14</sup> and de Lange<sup>15</sup> practically complete the list to which reference is made in literature on the salts of woman's milk up to the work of Schloss<sup>16</sup> in 1912.

The most important recent contribution on this subject has been made by the author last mentioned. His observations are much more numerous than those of any of the other writers. They were made on ten large individual samples of milk, eight of these being the total secretion for twenty-four hours; the other two were large samples collected during several successive days. In addition, two composite samples, obtained respectively from fifteen and sixteen women, were examined.

Schloss divides lactation into three periods: (1) colostrum period; (2) transition period extending from the colostrum to the end of the fourth week; (3) mature, or as he terms it, the period of "ripe" milk. He concludes that though the absolute values, especially of total ash and ash constituents, show great differences in individuals, the ratio of the separate constituents to one another is fairly constant. He was particularly struck by the parallelism of the total nitrogen and total ash values. From his findings he concludes that, with the exception of fat, all the constituents of milk stand in a fairly definite ratio to

9. Bunge: *Ztschr. f. Biol.*, 1874, x, 295.

10. Cammerer and Söldner: *Ztschr. f. Biol.*, xxxix, 173; xliv, 61.

11. Pelka: *Ztschr. f. Kinderh.*, 1911, ii, 442.

12. Blauberg: Quoted by Engel in Sommerfeld's *Handbuch der Milchkunde*, Wiesbaden, 1909, 800.

13. Abderhalden: Personal communication quoted by Schloss.

14. Birk: *Monatschr. f. Kinderh.*, 1910-11, ix, 595.

15. De Lange: *Ztschr. f. Biol.*, 1900, xl, 527.

16. Schloss: *Monatschr. f. Kinderh.*, 1910-11, ix, 636; x, 499.

one another. The high protein and high ash of colostrum milk, established by the earlier investigators, were confirmed by his findings. After the colostrum period these values sink rapidly, but no falling off was shown in his four mature cases taken between the twenty-sixth day and four and a half months. It was only in the milk of three women examined after ten months that a marked reduction was evident. There was no evidence to prove a relationship between the daily quantity and concentration.

In only one case were there high figures with a relatively small production of milk. The great variation in previously published figures, especially of calcium, he explains by the fact that most authors have analyzed only small portions of the twenty-four hours' secretion, and in many cases the milk was from mothers of rachitic children. Schloss concludes that there are not yet enough analyses, even including those of all previous workers, to establish a definite picture of the composition of woman's milk, particularly of the ash in the different periods of lactation.

Besides the work referred to on the entire ash, a number of authors have investigated separate salts of milk. Thus, a special study of the phosphorus has been made by Schlossmann.<sup>17</sup> His results from the analyses of the milk of thirty-one individual women show the following averages:

Colostrum period, 2 women.....	.0533
Transition period, 6 women.....	.0463
Mature period, 21 women.....	.0460
Late period, 2 women.....	.0360

The calcium content of milk in normal and various abnormal conditions has been studied quite exhaustively by Bahrdr and Edelstein.<sup>18</sup> They give results obtained by eight other investigators of normal milk, but the figures are chiefly from their own observations. They give the following values for CaO in the milk of eighty individual mothers of healthy children taken at the different periods of lactation, exclusive of authors whose results we have tabulated in our own paper. They may be grouped as follows:

Colostrum period, 4 women.....	.0476
Transition period, 23 women.....	.0397
Mature period, 51 women....	$\left\{ \begin{array}{ll} 1-3 \text{ months (7)} & .0489 \\ 3-5 \text{ months (32)} & .0411 \\ 6-8 \text{ months (6)} & .0385 \\ 8-10 \text{ months (6)} & .0392 \end{array} \right\} .0416$
Late period, 2 women.....	$\left\{ \begin{array}{ll} 14 \text{ months (1)} & .0452 \\ 16 \text{ months (1)} & .0341 \end{array} \right\} .0396$

In these figures it will be noted there is very little variation after the colostrum period.

17. Schlossmann: *Arch. f. Kinderh.*, 1905, xl, 1.

18. Bahrdr and Edelstein: *Jahrb. f. Kinderh.*, 1910, lxxii, Supplement, p. 16.

The iron content of woman's milk has also been studied by Bahrdt and Edelstein.<sup>19</sup> They employed the method of Neumann, in which the iron is brought down by a zinc reagent, filtered off, and dissolved in HCl; potassium iodid is then added and the freed iodine titrated with sodium thiosulphate. The amounts used for single determinations varied from about 708 c.c. to 1,300 c.c. The samples were made up of portions collected through periods of from two to four days. The milk of three nurses was studied at different times; the periods of lactation in all were between the twenty-fourth day and the sixth month. They obtained a range of .00012 to .00029 per cent. with an average value for  $\text{Fe}_2\text{O}_3$  of .00017 per cent. The individual variations were slight.<sup>20</sup>

These figures for iron correspond closely with those of Söldner who from examinations of two large samples of milk taken between the third and twelfth days gives values of .00021 and .00013—an average of .00017 per cent. Iron values given by several writers are considerably higher than those quoted; but many of them have been obtained from such small samples that the results of the analyses cannot be relied on.

From the great interest which has recently developed in the metabolism of the salts, it seemed to us desirable that the question of the composition of the ash in woman's milk should be studied anew and on a more extended scale than hitherto, and that further, an effort should be made to learn more of the individual variations in the different salts by the use of large individual samples.

The chief purpose of the investigation, the results of which are herewith presented, was a study of the composition of the ash in woman's milk at the different periods of lactation. Incidentally, we have made determinations of the other constituents of milk—fat, sugar and protein—and have made a study of the methods commonly employed in milk analysis.

In all, examinations have been made of thirty-two large individual samples—in most cases the entire twenty-four hours' secretion—and of six composite samples. Following the classification suggested by Schloss, these cases have been grouped as follows: In the "colostrum" period, two individual and three composite samples; in the "transition period," three individual and three composite samples; in the "mature"

19. Bahrdt and Edelstein: *Ztschr. f. Kinderh.*, 1910-11, i, 182.

20. Edelstein and Csonka (*Biochem. Ztschr.*, 1912, xxxviii, 14) have recently studied the iron content of cow's milk, using large samples for analysis. When milk was carefully drawn they obtained a range of values from 0.4 to 0.7 mg. per liter, with an average of 0.5. They conclude that the iron in cow's milk is only about one-third that in woman's milk. In point of fact the amount is so small as to be negligible.

period (one to nine months) seventeen individual samples. We have classed separately in a "late" period ten cases of milk from the tenth to the twentieth month. As we were endeavoring to secure normal values, only the milk of apparently healthy women with healthy children was taken.

The value of the observations it seems to us is enhanced by the fact of the large individual samples obtained for analysis. Of those who have previously studied this subject only Schloss appears to have appreciated the importance of securing for examination the twenty-four hours' secretion from a single individual. The observations we have made on the milk of the colostrum and transition periods have not quite the same importance as those of mature milk, since in a number of instances only composite samples were available for analysis.

The results of many of the published analyses of breast milk are open to criticism, since such small samples were used for study. This applies of course chiefly to the ash, but it has also some importance in the estimation of the other constituents. As already suggested, the methods employed by many authors are now known to be unreliable, while others make no mention of methods used. For comparison with our own results we have brought together the figures for ash analyses from the other investigators in this field whose methods could be relied on.

#### METHODS EMPLOYED

*Nitrogen.*—The Total N was determined in both liquid and dried samples by the Kjeldahl-Gunning method. The casein was precipitated by dilute acetic acid in a cold solution and the N determined in the filtrate, thus giving, first, the percentage of total protein which is casein, and secondly, the percentage of protein not precipitated by acetic acid. The latter figure necessarily includes any nonprotein nitrogenous substances which are present in the milk; there is evidence that such substances exist. In calculating the total protein as six and a quarter times the N there is therefore a slight error.

*Fat.*—The fat was determined in dried material by extraction with ether according to a modification of the Soxhlet method.

*Sugar.*—The question of the milk sugar content of the human milk does not seem yet to be definitely settled. Authors differ considerably in the range of values which they report, some, especially among the earlier investigators, giving figures below 6 per cent., while others obtain averages of above 7 per cent., and occasional figures run above 8 per cent.

Three general methods of sugar determinations have been employed: (1) Estimation by difference; (2) by the polariscope; (3) by some reduction method. In the first it has been customary to determine separately the fat, protein and ash and to regard the difference between the sum of these and the total dried weight as sugar. All the error in the analysis is thus thrown on the sugar. This method has been and still is much used, but is open to very obvious objections. Polariscope readings require considerable correction and are regarded as unreliable by several authors, including Reiss and Sommerfeld.<sup>21</sup> They may

21. Reiss and Sommerfeld in Sommerfeld's *Handbuch der Milchkunde*, 1909.

be too low because of the presence in the milk of substances which may cause rotation to the left.

Most of the figures for milk sugar reported have been obtained by some reduction method. Reduction methods may give too high figures because of the presence of other reducing substances than lactose. Schlossmann used a reduction method but obtained the value for the reduced copper by weighing instead of by titration. His range is from 5.2 to 10.9 per cent. Söldner used the same method and reports values from 5.35 to 7.52 per cent. If there is any difficulty due to the presence of reducing substances other than lactose, it is evidently not avoided by these investigators. Lust<sup>22</sup> gives for twenty-five women a range of 5.7 to 8.5 per cent., averaging 7.1 per cent. He also used a reduction method but made a colorimetric determination of the reduced copper. Schloss employed the titration method, but considers it inexact and does not include his results in his tables; his figures for sugar ranged from 6.38 to 7.9 per cent.

In our analyses the sugar was estimated after removal of the protein by boiling and then adding dilute acetic acid. The sugar was then determined by a titration method with Fehling's solution, in which the copper oxid is held in solution by potassium ferrocyanid. It was found that this method gave almost invariably higher results than the polariscope, but that it agreed very well with other reduction methods, including the Volhard. Both the reduction methods and the polariscope determinations are therefore also open to criticism. There cannot be said yet to have been devised a wholly satisfactory method for sugar determination in woman's milk.<sup>23</sup>

On the whole the indirect method of estimating the sugar by difference, although open to the most obvious objections, appeared in our work to give the most consistent results. If this method is followed, however, a definite procedure in drying must be employed. We have dried the samples to minimum weight over the water bath and then allowed them to come to constant weight in the air at room temperature. This last step was to make sure that the lactose when weighed should contain all its water of crystallization. Cammerer and Söldner showed that the dried matter at equilibrium with the air includes the water of crystallization of milk sugar, but that if milk is brought to a constant weight in vacuo at 98 C. the lactose is in an anhydrous condition. The figures given in our tables represent the lactose with its water of crystallization. The lactose in an anhydrous form weighs 5 per cent. less. Most authors do not state which form of lactose their figures indicate. In our table we have given both the figures obtained by the reduction method and also those in which the estimation is by difference.

*Ash.*—The greater part of the twenty-four hours' secretion was dried on a steam bath until it reached a constant weight in equilibrium with room temperature and humidity. In this dried material the total ash and the separate ash constituents were determined. The method of ashing is of considerable importance. The one employed is that described by Karl Stölte;<sup>24</sup> a sufficient sample

22. Lust: *Monatschr. f. Kinderh.*, 1912, vi, 236.

23. Since the greater part of this work was completed, a new method for removing the protein from milk, preparatory to sugar determination, has been suggested by Hill of Ithaca (*Jour. Biol. Chem.*, March, 1915). To precipitate the protein after boiling, colloidal iron is added to the specimen of milk. This method was proposed for cow's milk. In applying this to woman's milk we have found it advantageous to add a few drops of a saturated solution of magnesium sulphate. In certain samples of milk it is impossible to obtain a clear filtrate with the acetic acid precipitation. In such cases the new procedure is of much value. By means of it we have never failed to obtain a clear filtrate. The application of this method, however, would affect the result in only a very small number of the analyses given in this paper.

24. Stölte: *Biochem. Ztschr.*, 1911, xxxv, 104.

of the dried substance, finely ground, is weighed into a platinum dish, which is set on pieces of broken pipe-clay inside a porcelain dish of a diameter 1 to 2 inches greater than that of the platinum dish. Low heat from a large-sized Teklu burner is applied to the porcelain dish until the material is well charred; then the heat is gradually increased to the greatest possible point. When most of the black has disappeared, the platinum dish is covered by a piece of platinum foil and ignition continued until ashing is completed. This method seems to be especially advantageous in connection with the determination of sodium and potassium, since it is found that pure sodium chlorid and potassium chlorid subjected to this treatment for hours lose no weight whatever. Ash obtained in this way was used for the determination of calcium, magnesium, phosphorus, sodium and potassium.

To avoid the possibility of a slight loss of chlorine during the breaking down of the organic compounds, this constituent of the milk was determined directly in the dried material. We have followed the method of removal of the protein by ferric alum and nitric acid, and titration of the chlorids in the filtrate according to Volhard. This is similar to the method chosen by Schloss after he had carefully tested it in comparison with other methods commonly used.

*Calcium, magnesium, sodium, potassium and phosphorus* were all determined by the usual methods. Calcium was precipitated as oxalate and weighed as oxid. Magnesium was precipitated as magnesium ammonium phosphate and weighed as pyrophosphate. Sodium and potassium were separated as chlorids and the potassium determined in the combined chlorids by precipitation with platinic chlorid. By the use of the Stölte method of ashing just described, the danger of volatilization of potassium and sodium chlorids, both in the initial ashing and at the stage of driving off ammonium salts, is entirely avoided. Unless this or some similar precaution is taken the values obtained for potassium and sodium are absolutely unreliable. Phosphoric acid was precipitated as ammonium phosphomolybdate; this was dissolved by ammonia and magnesium ammonium phosphate, precipitated by magnesia mixture and weighed as pyrophosphate.

The fat, sugar, protein and total ash in milk of the different periods are given in Table 1.

*Colostrum.*—The chief characteristic of the milk of the colostrum period is the high protein and the high total ash. The ash in one sample (No. 3) was so much lower than all the others that it must be regarded as an exceptional individual variation. Excluding this one the average ash for the period was 0.3077, the average protein 2.25 per cent. These figures correspond fairly well with those published by other observers. The specific gravity differs little from that of the milk of other periods.

Our values for sugar are somewhat higher than those reported by other investigators. The sugar figure was obtained by reduction in but a single sample; in the others it was estimated by difference. The reason for this was that our chief purpose was a study of the salts of milk, and it was sometimes impossible to do both determinations with the amount of milk which could be obtained for examination. The fat for all the samples analyzed averaged 3.15 per cent. But one of the individual samples which was taken at the very end of the colostrum period was unusually high, 4.43 per cent. An average of the remain-

TABLE 1.—PERCENTAGE COMPOSITION OF WOMAN'S MILK

## A. COLOSTRUM PERIOD (1 TO 12 DAYS)

No	Age of Woman, Yrs.	Age of Child, Days	No. of Child	Sample	Amt. in c.c.	Sp. Gr.	Total Solids	Fat	Sugar by		Protein			Ash
									Reduction	Difference	Total	Casein	Albumin	
1	19-21	3-4	....	Composite, 5 women	295	.....	12.87	2.85	....	7.66	2.06	..	....	.2960
2	18-25	3-5	....	Composite, 6 women	960	1.032	12.68	3.30	6.50	7.09	1.96	.26	1.70	.3312
3	....	5-7	....	Individual	320	1.035	12.83	2.13	....	7.92	2.60	...	....	.1747
4	....	5-8	....	Individual	240	1.032	15.05	4.43	....	7.16	2.44	...	....	.2921
5	20-25	5-12	....	Composite, 4 women	210	.....	13.67	3.05	....	8.12	2.19	...	....	.3117

## B. TRANSITION PERIOD (12 TO 30 DAYS)

6	16-21	12-30	....	Composite, 4 women	285	.....	15.66	5.64	....	8.18	1.61	...	....	.2335
7	32	14	....	Individual	215	1.032	10.36	1.33	....	7.76	1.06	...	....	.2132
8	20	15-18	....	Composite, 2 women	490	1.032	12.74	3.89	....	7.24	1.36	...	....	.2471
9	19-32	14-28	....	Composite, 5 women	175	.....	14.18	4.01	....	7.88	1.99	...	....	.3042
10	18	21	....	Individual	175	.....	13.77	....	....	....	1.42	...	....	.2262
11	19	21	....	Individual, 24 hours	975	1.032	13.66	3.96	7.80	7.73	1.75	.45	1.30	.2204

## C. MATURE PERIOD (1 TO 9 MONTHS)

		Mos.												
12	18	1	1	Individual, 48 hours	1,075	1.024	9.81	3.07	5.54	5.44	1.17	.37	.80	.1825
13	32	2	2	Individual, 24 hours	975	1.032	10.30	1.86	8.20	7.19	1.03	.40	.63	.2200
14	24	2	3	Individual, 24 hours	1,100	1.031	11.82	2.83	7.86	7.73	1.07	.41	.66	.1902
15	26	3	2	Individual, 36 hours	1,025	1.033	10.54	1.67	8.38	7.82	0.88	.04	.84	.1717
16	25	3	2	Individual, 24 hours	800	1.036	12.16	2.93	7.05	8.06	0.96	.46	.50	.2127
17	23	3	1	Individual, 24 hours	900	.....	12.05	2.87	7.78	7.73	1.23	.51	.72	.2135
18	32	3	2	Individual, 24 hours	850	.....	14.43	4.53	7.33	8.18	1.50	.64	.86	.2254
19	27	3½	2	Individual, 24 hours	950	1.031	13.11	3.89	8.38	7.72	1.26	.46	.80	.2433
20	23	3¾	1	Individual, 24 hours	880	.....	13.45	3.74	7.27	8.36	1.16	.52	.64	.1914
21	39	4	2	Individual, 24 hours	1,050	1.033	11.31	2.59	8.45	7.50	1.01	.34	.67	.2090
22	23	4	1	Individual, 24 hours	975	1.032	12.18	3.19	8.11	7.65	1.13	.36	.77	.2141
23	26	5	1	Individual, 24 hours	975	1.031	12.38	3.76	8.38	7.29	1.10	.45	.65	.2281
24	37	6	2	Individual, 48 hours	975	1.033	11.53	2.15	8.10	8.01	1.18	.36	.82	.1922
25	30	6	4	Individual, 36 hours	1,150	1.030	12.50	3.26	7.98	8.05	1.12	.53	.59	.1590
26	30	7	2	Individual, 24 hours	840	.....	14.13	5.48	7.48	7.11	1.29	.52	.77	.2462
27	22	5½	1	Individual, 48 hours	960	1.033	13.20	4.42	7.75	7.26	1.31	.53	.78	.2158
28	28	9	1	Individual, 2 days	960	1.033	11.86	3.27	7.60	7.16	1.23	.42	.81	.1974



TABLE 1.—(Continued)

D. LATE PERIOD (10 TO 20 MONTHS)

No.	Age of Woman, Yrs.	Age of Child, Mos.	No. of Child	Sample	Amt. in c.c.	Sp. Gr.	Total Solids	Fat	Sugar by		Protein			Ash
									Reduction	Difference	Total	Casein	Albumin	
29	31	10	4	Individual, 4 days	450	.....	12.25	3.92	7.92	8.02	1.00	.30	.70	.....
30	25	10½	1	Individual, 2 days	465	1.031	12.29	3.21	7.58	8.00	0.84	...	...	.2148
31	23	11¼	1	Individual, 2 days	480	1.036	10.00	0.97	....	7.77	1.05	...	...	.2107
32	33	12	3	Individual, 3 days	350	1.031	12.16	2.43	7.65	8.36	1.15	.35	.80	.2141
33	30	12½	4	Individual, ½ day	650	1.032	12.38	3.71	7.57	7.58	0.92	.40	.52	.1728
34	26	12½	..	Individual, 1 day	690	1.028	12.77	3.87	7.01	7.66	1.03	.42	.61	.2108
35	..	14	..	Individual, 3 days	560	.....	10.63	2.60	7.14	7.31	1.14	.05	1.09	.1790
36	30	15	4	Individual, ½ day	640	1.029	15.56	6.20	7.10	8.60	1.20	.64	.56	.1675
37	..	18	..	Individual, 5 days	615	1.030	12.30	3.51	7.47	7.40	1.17	...	...	.2251
38	35	20	6	Individual, 3 days	690	1.033	11.44	2.70	7.77	7.34	1.22	.16	1.06	.1855

ing four analyses, including three composite and one individual sample, was 2.83 per cent., which is probably much nearer the usual fat content of colostrum milk. It corresponds with the results obtained by others.

*Transition.*—In the transition period there is noted a striking reduction both in protein and total ash; but a considerable rise in the fat. Here again the percentage of fat in one specimen (No. 7) was so low as clearly to be an exceptional individual variation. The average for the remaining one individual and three composite samples was 4.37 per cent. The average values for the other elements were sugar 7.74; protein, 1.56; ash, 0.2581 and total solids, 13.39 per cent.

While these figures are too few in number to be regarded as more than suggestive, they indicate that the secretion of woman's milk is richer in fat, in protein, in salts and in total solids in the early weeks of lactation than at a later period. It corresponds also to the needs of the infant during the period of his most rapid growth. This, as one would expect, is most striking in the case of the ash and the protein.

*Mature.*—The figures for mature milk are from seventeen large individual samples—usually the twenty-four hours' secretion. Though the number of cases is small, the figures have a value which does not attach to those obtained from a study of small samples. They were all from healthy women whose infants were thriving; they were all upon a mixed diet. The age and the number of the child are given in the table. As would be expected, the figures show considerable indi-

vidual variation in all the elements; this is least in the protein and greatest in the fat. The figures for sugar are given both as obtained directly by reduction and as estimated, in the more common way, by difference. Compared with the early or transition period there is noted a fall in the total solids which affects all the elements except the sugar, but is most noteworthy in the protein and the ash.

For comparison we at first divided these into two groups: the first group of nine samples of one to four months' milk; the second of eight samples of four to nine months' milk. But the differences in the individual samples and in the averages of these two periods was so slight that a separate grouping seemed unnecessary.

The individual variations in this period are most marked in the fat, the range being from 1.67 to 5.48 per cent. The smallest variation is seen in the sugar. The lowest value found was 5.54 per cent. Except for this one specimen the range was between 7.05 and 8.38 per cent. obtained by reduction, and 7.11 and 8.36 per cent. by difference. In the main, therefore, the values obtained for sugar by the two methods do not differ greatly. The range for the total protein is from 0.88 to 1.5 per cent.; the figures in all but three of the seventeen samples fall between 1 and 1.3 per cent. The relation of the casein and albumin continues fairly uniform throughout both periods. The range in the total ash is between 0.1590 and 0.2433 per cent., but the greater number of the samples fall between 0.18 and 0.22 per cent.

In the colostrum period the relation of the ash to total protein is 1:7; in the transition period it is 1:6; throughout the mature period it is about 1:5, or the same ratio as exists in cow's milk.

*Late.*—Greater interest attaches to a study of the ten samples of late milk—tenth to twentieth month, for so few observations on milk of this period have been published. There are two or three exceptional findings, but as a group the milks for this period show no constant or essential differences in any of their constituents from those of the mature period. The marked fall in the protein and ash noted by some observers was not regularly seen in our cases. In but two of the ten cases was the protein low, while in five of the ten cases the ash was higher than the average of the mature period.

Excluding the three very exceptional individual variations mentioned, two of fat and one in total ash, occurring in the colostrum and transition periods, the average percentage composition of the milk for each of the different periods is as shown in Table 2.

We have brought together in Table 3 the results of the analyses found in medical literature which bear on the composition of the ash of normal woman's milk. The cases have been grouped according to the division of Schloss to whose work we are much indebted. The

total number of analyses we have been able to collect is but twenty-eight, even though we include five which are either incomplete or open to some question.

The results of our own observations on the different salts which make up the ash are given in Table 4, classified according to periods.

The variations in the total ash for the different periods have already been considered. The striking fall in the ash value continues only from the colostrum through the transition period; after this little regular variation is shown by these figures. In the samples in which the total ash was exceptionally low, while there was a reduction in all the ash constituents, it was most marked in the  $\text{Na}_2\text{O}$  and  $\text{K}_2\text{O}$ .

Of all the ash constituents the percentage of  $\text{CaO}$  continues most nearly constant throughout. This is shown not only by periods but by individual samples. In only two of the entire thirty-eight samples analyzed did the value for this element differ very widely from the

TABLE 2.—PERCENTAGE COMPOSITION OF WOMAN'S MILK BY PERIODS

Period	No. of Analyses	Fat	Sugar	Protein	Casein	Albumin	Ash	Total Solids
Colostrum, (1-12 da.).....	5	2.83	7.59	2.25	....	....	.3077	13.42
Transition, (12-20 da.).....	6	4.37	7.74	1.56	....	....	.2407	13.39
Mature, (1-9 mos.).....	27	3.26	7.50	1.15	.43	.72	.2062	12.16
Late, (10-20 mos.).....	10	3.16	7.47	1.07	.32	.75	.1978	12.18

average. Both these (Nos. 15 and 17) were individual samples of three months' milk; these two represent the range of values found, viz., 0.0295 and 0.0702 per cent.

The figures for  $\text{MgO}$  show a wider variation, not only for the different periods, but in the individual samples. The fall from the highest value in the colostrum period to the lowest in the transition period is without evident explanation. The lowest value, 0.0036 per cent., was in an individual sample of transition milk (No. 10), the highest, 0.0161, was in an individual sample in the colostrum period (No. 4).

The figures for  $\text{P}_2\text{O}_5$  like those for  $\text{CaO}$  do not show wide variations either in the different periods or in the separate samples. The values are somewhat higher in the colostrum and transition periods; but they show no regular change till the late period when the smallest average is seen. The range is from 0.0526, an individual colostrum sample (No. 3) to 0.0212, an individual sample of a six months' milk (No. 25) in which also the total ash was the lowest met with in our observations.

TABLE 3.—DISTRIBUTION OF THE ASH—GRAMS PER 100 C.C. OF MILK

## A. COLOSTRUM PERIOD

No.	Author	Age of Woman, Yrs.	Age of Child, Days	Sample	Amt. in c.c.	Total Ash	Percentage Composition of the Ash					
							CaO	MgO	P <sub>2</sub> O <sub>5</sub>	Na <sub>2</sub> O	K <sub>2</sub> O	Cl
1	Söldner.....	..	5-8	Composite, 2 women	.....	.3497	.0320	.0068	.0320	.0470	.1370	.0710
2	Söldner.....	..	5-9	Composite, 6 women	.....	.2894	.0100	.0052	.0320	.0280	.1000	.0660
3	Söldner.....	..	5-9	Composite, 6 women	.....	.3382	.0420	.0077	.0280	.0370	.0570	.0920
4	De Lange*..	..	1-10	Composite, 10 women	.....	.....	.....	.....	.....	.0650	.0640	.....
	De Lange....	..	4-10	Composite, 23 women	.....	.....	.0410	.0060	.0580	.....	.....	.0680
5	Schloss.....	22	11-13	Individual.	.....	.3048	.0335	.0080	.0380	.0532	.0735	.0892
6	Birk.....	..	.....	.....	.....	.2814	.0360	.0063	.1137	.0544	.0770	.....
Averages...							.0375	.0074	.0380	.0374	.0607	.0772
							11.9	2.1	10.5	16.0	30.5	24.7

## B. TRANSITION PERIOD

No.	Author	Age of Woman, Yrs.	Age of Child, Days	Sample	Amt. in c.c.	Total Ash	Percentage Composition of the Ash					
							CaO	MgO	P <sub>2</sub> O <sub>5</sub>	Na <sub>2</sub> O	K <sub>2</sub> O	Cl
7	Söldner.....	..	7-12	Composite, (of several women)	.....	.2620	.0370	.0070	.0330	.0340	.0790	.0570
8	Söldner.....	..	22-43	Composite, (of several women)	.....	.2185	.0410	.0044	.0320	.0170	.0680	.0360
9	Schloss.....	22	14-17	Individual	.700	.2331	.0400	.0069	.0393	.0338	.0678	.0425
10	Schloss.....	22	26	Individual	1.180	.1904	.0355	.0081	.0393	.0192	.0588	.0310
11	Bunge.....	..	15	Individual	.....	.2219	.0328	.0064	.0473	.0232	.0780	.0438
12	Bunge.....	..	18	Individual (same)	.....	.2187	.0343	.0065	.0469	.0257	.0703	.0445
Averages...							.0364	.0062	.0396	.0258	.0698	.0424
							16.4	2.7	17.9	11.3	31.0	18.7

		Mos. 2-3				.0180	.0065	.0385	.0253	.0735	.0468	19.1	2.5	22.9	9.9	31.2	18.3
13	Abderhalden	..	.....	.....	.....	.0387	.0094	.0131	.0219	.0522	.0255	20.5	4.9	22.8	11.6	27.6	13.3
14	Schloss.....	21	2½	Individual	2,600	.0267	.0116	.0701	.0200	.0650	.0425	23.1	4.7	20.4	8.1	26.4	17.3
15	Schloss.....	27	3	Individual	790	.0370	.0160	.0342	.0192	.0549	.0308	20.0	5.4	18.5	10.3	29.7	16.7
16	Schloss.....	19	3½	Individual	1,360	.0155	.0087	.0116	.0210	.0608	.0111	21.8	4.1	19.9	10.0	29.1	19.7
17	Schloss.....	27	4½	Individual	1,680	.0386	.0076	.0147	.0162	.0529	.....	20.1	3.9	23.3	8.4	27.6	....
18	Schloss.....	..	.....	Composite	.....	.0380	.0073	.0383	.0196	.0536	.0312	20.7	3.9	20.8	10.6	29.1	16.9
19	Schloss.....	..	.....	Composite	.....	.0350	.0060	.0260	.0180	.0540	.0330	19.4	3.5	14.4	10.1	32.8	18.5
20	Söldner.....	..	3½	Individual	.....	.0304	.0048	.0294	.0049	.0640	.0294	19.8	3.1	14.7	2.1	34.7	11.7
21	Blauberg....	..	.....	.....	.....	.0174	.....	.0387	.0258	.0848	.0291	25.9	...	21.1	14.1	46.3	16.0
22	Pelka.....	..	.....	Composite	.....	.0328	.....	.0470	.0165	.0613	.0244	13.2	...	18.1	6.6	25.9	9.8
23	Pelka.....	..	.....	Composite	.....	.....	.....	.....	.....	.....	.....	17.4	3.2	14.8	7.9	33.7	15.5
24	Backhaus and Cronhelm	..	.....	.....	.....	.....	.....	.....	.....	.....	.....	15.5	2.1	11.8	15.9	27.3	23.9
25	Backhaus and Cronhelm	..	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
Averages...			.....	.....	.1555	.0116	.0082	.0469	.0189	.0632	.0340	19.5	3.7	18.5	10.3	30.7	17.5
D. LATE PERIOD																	
26	Schloss.....	21	11	Individual	1,650	.0285	.0073	.0319	.0177	.0140	.0028	19.3	4.9	23.6	12.3	29.8	15.1
27	Schloss.....	..	11½	Individual	720	.0305	.0073	.0376	.0156	.0419	.0255	20.2	4.8	21.9	10.4	29.8	16.9
28	Schloss.....	26	14½	Individual	1,675	.0280	.0082	.0431	.0162	.0465	.0251	28.0	3.9	27.7	10.1	29.9	16.1
Averages...			.....	.....	.1512	.0230	.0069	.0385	.0165	.0451	.0211	22.5	4.1	25.4	11.0	29.8	16.1

\* De Lange's work is usually quoted as a single, complete analysis. The original publication shows that part of the ash was determined from one sample, and the other elements from a second.

† Birk's figures are often quoted and hence are introduced. His value for  $P_2O_5$  differs so widely from other published figures, as well as ours, that we have omitted this case in computing the averages.

‡ By addition, the figure by determination is not given in the original paper.

TABLE 4.—DISTRIBUTION OF THE ASH—GRAMS PER 100 C.C. OF MILK

A. COLOSTRUM PERIOD											
No.	Age of Woman, Yrs.	Age of Child, Days	No. of Child	Sample	Total Ash	CaO	MgO	P <sub>2</sub> O <sub>5</sub>	Na <sub>2</sub> O	K <sub>2</sub> O	Cl
1	19-21	3-4	....	Composite, 5 women	.2960	.0431	.0092	.0308	*	*	.0640
2	18-25	3-5	....	Composite, 6 women	.3312	.0527	.0053	.0369	.0453	.0938	.0744
3	.....	5-7	....	Individual	.1747	.0476	.0076	.0526	*	*	.0304
4	.....	5-8	....	Individual	.2921	.0415	.0161	.0501	*	*	.0693
5	20-25	5-12	....	Composite, 4 women	.3117	.0382	.0125	.0347	*	*	.0462
B. TRANSITION PERIOD											
6	16-21	12-30	....	Composite, 4 women	.2335	.0450	.0071	.0497	*	*	.0590
7	32	14	....	Individual	.2132	.0338	.0049	.0308	*	*	.0639
8	20	15-18	....	Composite, 2 women	.2471	.0437	.0073	.0370	.0392	.0585	.0598
9	19-32	14-28	....	Composite, 5 women	.3042	.0498	.0067	.0397	*	*	.0955
10	18	21	....	Individual	.2262	.0289	.0036	.0419	.0136	.0811	.0368
11	19	21	....	Individual, 24 hours	.2204	.0343	.0051	.0433	.0239	.0731	.0334
C. MATURE PERIOD											
		Mos.									
12	18	1	1	Individual, 48 hours	.1825	.0413	.0052	.0265	.0183	.0480	.0251
13	32	2	2	Individual, 24 hours	.2200	.0497	.0092	.0276	.0131	.0638	.0423
14	24	2	3	Individual, 24 hours	.1902	.0414	.0084	.0317	.0148	.0502	.0364
15	26	3	2	Individual, 36 hours	.1717	.0295	.0057	.0239	.0214	.0494	.0352
16	25	3	2	Individual, 24 hours	.2127	.0459	.....	.0431	*	*	.0383
17	23	3	1	Individual, 24 hours	.2135	.0702	.0089	.0409	.0145	.0366	.0378
18	32	3	2	Individual, 24 hours	.2254	.0536	.0106	.0392	.0143	.0618	.0313
19	27	3½	2	Individual, 24 hours	.2433	.0555	.0091	.0440	.0175	.0714	.0378
20	23	3¾	1	Individual, 24 hours	.1914	.0503	.0090	.0310	.0250	.0504	.0318
21	39	4	2	Individual, 24 hours	.2090	.0456	.0067	.0331	.0129	.0599	.0437
22	23	4	1	Individual, 24 hours	.2141	.0535	.0077	.0366	.0112	.0633	.0313
23	26	5	1	Individual, 24 hours	.2281	.0545	.0072	.0386	.0126	.0661	.0320
24	37	6	2	Individual, 48 hours	.1922	.0412	.0082	.0299	.0158	.0582	.0315
25	30	6	4	Individual, 36 hours	.1560	.0354	.0072	.0212	.0031	.0545	.0304
26	30	7	2	Individual, 24 hours	.2402	.0513	.0084	.0514	.0133	.0644	.0376
27	22	8½	1	Individual, 48 hours	.2158	.0430	.0092	.0380	.0169	.0688	.0441
28	38	9	1	Individual, 2 days	.1974	.0426	.0097	.0301	.0204	.0531	.0358

\* The values for Na and K in the earlier samples have not been included in the table because the method of ashing the dried material, and later of igniting to drive off ammonium salts, was one in which a slight loss of Na and K by volatilization is possible. The Stolte method described elsewhere in the paper was used in the case of most of the other samples.

TABLE 4.—(Continued)

## D. LATE PERIOD

No. Woman,	Age of Yrs.	Age of Child, Mos.	No. of Child	Sample	Total Ash	CuO	MgO	P <sub>2</sub> O <sub>5</sub>	Na <sub>2</sub> O	K <sub>2</sub> O	Cl
29	31	10	4	Individual, 4 days	.....	.....	.....	.0281	.0126	.0469	.0439
30	25	10½	1	Individual, 2 days	.2148	.0433	.0097	.0282	.0282	.0490	.0474
31	23	11¼	1	Individual, 2 days	.2107	.0483	.0045	.0348	.0133	.0594	.0405
32	33	12	3	Individual, 3 days	.2141	.0405	.0071	.0332	.0315	.0673	.0570
33	30	12½	4	Individual, ½ day	.1728	.0390	.0059	.0227	.0188	0.504	.0339
34	26	12½	....	Individual, 1 day	.2108	.0320	.0072	.0297	.0338	.0551	.0521
35	..	14	....	Individual, 3 days	.1790	.0396	.0093	.0270	.0134	.0545	.0441
36	30	15	4	Individual, ½ day	.1675	.0348	.0093	.0296	.0146	.0556	.0301
37	..	18	....	Individual, 5 days	.2251	.0461	.0054	.0422	.0151	.0576	.0500
38	35	20	6	Individual, 3 days	.1855	.0280	.0048	.0284	.0135	.0794	.0433

## AVERAGES FOR THE DIFFERENT PERIODS

	No. of Analyses	Total Ash	CaO	MgO	P <sub>2</sub> O <sub>5</sub>	Na <sub>2</sub> O	K <sub>2</sub> O	Cl
Colostrum (1-12 days).....	5	.3077	.0446	.0101	.0410	.0453	.0938	.0568
Transition (12-30 days).....	6	.2407	.0409	.0057	.0404	.0255	.0709	.0589
Early mature (1-4 months)..	9	.2056	.0486	.0082	.0342	.0154	.0539	.0351
Middle mature (4-9 months)	8	.2069	.0458	.0074	.0345	.0132	.0609	.0358
Late milk (10-20 months)....	10	.1978	.0390	.0070	.0304	.0195	.0575	.0442

For reasons already mentioned (see note to Table 4) we have reported only a single figure for Na<sub>2</sub>O and K<sub>2</sub>O in the colostrum period, and but three in the transition period. These figures indicate the highest value for Na<sub>2</sub>O in the colostrum period, next in the transition period, while during the early and latter part of the mature period it falls to less than one-third the amount. It is noteworthy that three of the ten late milks show a very high sodium figure; the figures for the other samples correspond with those of the mature period. The extreme individual variations of sodium are considerable in the mature period—from 0.0031 (No. 25) to 0.0250 (No. 20); but in the remaining cases of this period the value for this constituent is very close to the average.

Like Na<sub>2</sub>O the value for K<sub>2</sub>O is highest in the colostrum period and next in the transition period, but after this time it is quite uniform even in the late period. The individual variations are smaller than in the case of the sodium.

TABLE 5.—PERCENTAGE COMPOSITION OF THE ASH

A. COLOSTRUM PERIOD											
No.	Age of Woman, Yrs.	Age of Child, Days	No. of Child	Sample	Total Ash	CaO	MgO	P <sub>2</sub> O <sub>5</sub>	Na <sub>2</sub> O	K <sub>2</sub> O	Cl
1	19-21	3-4	....	Composite, 5 women	.2960	14.6	3.1	10.4	....	....	21.6
2	18-25	3-5	....	Composite	.3312	15.9	1.6	11.2	13.7	28.1	22.5
3	....	5-7	....	Individual	.1747*	27.2	4.4	30.1	....	....	17.4
4	....	5-8	....	Individual	.2921	14.2	5.5	17.2	....	....	23.7
5	20-25	5-12	....	Composite, 4 women	.3117	12.3	4.0	11.1	....	....	14.8
B. TRANSITION PERIOD											
6	16-21	12-30	....	Composite, 4 women	.2335	19.3	3.0	21.3	....	....	25.3
7	32	14	....	Individual	.2132	15.9	2.3	14.4	....	....	30.0
8	20	15-18	....	Composite, 2 women	.2471	17.7	3.0	15.0	15.9	23.5	24.2
9	19-32	14-28	....	Composite, 5 women	.3042	16.4	2.2	13.1	....	....	31.4
10	18	21	....	Individual	.2262	17.2	1.6	18.5	6.0	35.8	16.3
11	19	21	....	Individual, 24 hours	.2204	15.6	2.3	19.6	10.8	33.2	15.1
C. MATURE PERIOD											
		Mos.									
12	18	1	1	Individual, 48 hours	.1825	22.6	2.8	14.5	10.0	26.3	13.8
13	32	2	2	Individual, 24 hours	.2200	22.6	4.2	12.6	6.0	29.0	19.0
14	24	2	3	Individual, 24 hours	.1902	21.8	4.4	16.7	7.8	26.4	19.2
15	26	3	2	Individual, 36 hours	.1717	17.2	3.3	13.9	12.5	28.8	20.5
16	25	3	2	Individual, 24 hours	.2127	21.6	1.3	20.2	....	31.9	18.0
17	23	3	1	Individual, 24 hours	.2135	32.9	4.2	19.2	6.8	17.1	17.7
18	32	3	2	Individual, 24 hours	.2254	23.8	4.7	17.4	6.3	27.4	13.9
19	27	3½	1	Individual, 24 hours	.2433	22.8	3.7	18.1	7.2	29.4	15.5
20	23	3¾	2	Individual, 24 hours	.1914	26.3	4.7	16.2	13.1	26.3	16.6
21	39	4	1	Individual, 24 hours	.2090	21.8	3.2	15.8	6.2	28.7	20.9
22	23	4	1	Individual, 24 hours	.2141	25.0	3.6	17.1	5.2	29.6	14.6
23	26	5	2	Individual, 24 hours	.2281	23.9	3.2	16.9	5.5	29.0	14.0
24	37	6	4	Individual, 48 hours	.1922	21.4	4.3	15.6	8.2	30.3	16.4
25	30	6	2	Individual, 36 hours	.1590	22.3	4.5	13.3	2.0	34.3	19.1
26	30	7	1	Individual, 24 hours	.2402	21.4	3.5	21.4	5.5	26.8	15.7
27	22	8½	1	Individual, 48 hours	.2158	19.9	4.3	17.6	7.8	31.8	20.6
28	28	9	....	Individual, 2 days	.1974	21.6	4.9	15.3	10.4	27.0	18.2

\* This is so exceptional a figure that the values are excluded in computing the averages.



TABLE 5.—(Continued)

D. LATE PERIOD

No. Woman,	Age of Yrs.	Age of Child, Mos.	No. of Child	Sample	Total Ash	CaO	MgO	P <sub>2</sub> O <sub>5</sub>	Na <sub>2</sub> O	K <sub>2</sub> O	Cl
29	31	10	4	Individual, 4 days	†						
30	25	10½	1	Individual, 2 days	.2148	20.2	1.5	13.1	13.1	22.8	22.1
31	23	11¼	1	Individual, 2 days	.2107	22.9	2.1	16.5	6.3	28.2	19.2
32	33	12	3	Individual, 3 days	.2141	18.9	3.3	15.5	14.7	31.4	26.6
33	30	12½	4	Individual, ½ day	.1728	22.6	3.1	13.2	10.9	29.2	19.6
34	26	12½	....	Individual, 1 day	.2108	15.2	3.4	14.1	16.1	26.2	24.8
35	..	14	....	Individual, 3 days	.1790	22.1	5.2	15.1	7.5	30.4	24.6
36	30	15	4	Individual, ½ day	.1675	20.8	5.6	17.7	8.7	33.2	18.0
37	..	18	....	Individual, 5 days	.2251	20.4	2.4	18.8	6.7	25.6	22.2
38	35	20	6	Individual, 3 days	.1855	15.1	2.6	15.3	7.3	42.8	23.4

† Percentage could not be calculated as total ash was not determined.

## AVERAGE PERCENTAGE COMPOSITION OF ASH FOR THE DIFFERENT PERIODS

	CaO	MgO	P <sub>2</sub> O <sub>5</sub>	Na <sub>2</sub> O	K <sub>2</sub> O	Cl
Colostrum.....	14.2	3.5	12.5	13.7	28.1	20.6
Transition.....	17.0	2.4	16.9	10.9	30.8	22.9
Mature.....	23.3	3.7	16.6	7.2	28.3	16.5
Late.....	19.8	3.6	15.5	10.1	28.8	22.3

The figures for Cl vary much like the two constituents just mentioned; in all periods they bear a very close relation to the combined values of Na<sub>2</sub>O and K<sub>2</sub>O, indicating that it is combined as chlorids of sodium and potassium in the milk. The P<sub>2</sub>O<sub>5</sub> and the CaO have also a close relationship in all periods, indicating their existence in milk as calcium phosphate.

Considering the milk by periods, we note that the high ash of the colostrum period is chiefly due to the higher values for Na<sub>2</sub>O and K<sub>2</sub>O; the values for CaO and P<sub>2</sub>O<sub>5</sub> differing but slightly from those of the later periods. The values of the transition period show a further fall in Na<sub>2</sub>O and K<sub>2</sub>O and Cl, but little change in the other elements.

No constant or essential differences are seen in the values for the salts which make up the ash in either the early or latter part of the mature period, nor, in fact, even in the late period. These were grouped separately for the purpose of determining whether such a difference existed. Even in the late period the values show very little difference from those in the preceding period.

Some details of the women furnishing the late milks are interesting. In four instances (Nos. 29, 33, 34 and 36) the supply was still abundant and nursing was being carried on successfully (Nos. 33 and 36 were from the same woman). Three samples (Nos. 30, 35, 38) were taken at the very end of a previously successful lactation, two or three days' pumping being usually required to obtain sufficient milk for analysis. In three cases (Nos. 31, 32, 37) there was still a good supply of milk, the infants being partly nursed and partly fed.

From a practical standpoint the best idea of the salts of woman's milk is obtained from a study of the percentage composition of the ash. This is given in the Table 5.

A comparison of the percentage composition of the salts of woman's milk, mature period, with those of cow's milk is highly instructive. The figures for cow's milk are the averages of nine analyses of our own, made of milk from mixed herds.

TABLE 6.—COMPARISON OF THE PERCENTAGE COMPOSITION OF THE ASH OF WOMAN'S AND COW'S MILK

	CaO	MgO	P <sub>2</sub> O <sub>5</sub>	Na <sub>2</sub> O	K <sub>2</sub> O	Cl
Mature woman's milk.....	23.3	3.7	16.6	7.2	28.3	16.5
Cow's milk.....	23.5	2.8	26.5	7.2	24.9	13.6

The close correspondence between these figures is very striking. In all the constituents except P<sub>2</sub>O<sub>5</sub> the percentages of the different salts in the two milks are practically the same. The higher proportion of phosphorus in cow's milk is due to the large amount in the casein. Though the *proportions* of the different salts of the ash in cow's milk are so nearly those of woman's milk, the *amount* in cow's milk is about three and a half times as great. Unless, therefore, cow's milk has been diluted with more than twice its volume, the amount of these inorganic constituents furnished to the infant is equal to that which he receives in woman's milk. The addition of lime or other inorganic salts to cow's milk because they are lacking in amount is therefore quite unnecessary in infant feeding.

A general comparison of the results of our analyses with those of the other authors cited shows a general agreement in most of the essential points. There is, however, less variation between the findings in our individual cases than between the findings of the different investigators who have made but a small number of analyses. It is not unlikely that differences in methods or in technic may be responsible, in part, at least, for some of these wider variations. We feel that enough analyses of the salts of normal woman's milk have now been

made to afford a basis for comparison with abnormal milks studied in connection with metabolism observations.

There remains for brief discussion a consideration of the iron content of milk. For reasons already given, we have not undertaken a study of this part of the subject. The results of the analyses of the authors quoted in the earlier part of the paper indicate that the figures previously given for iron are too high; that woman's milk contains but 1.7 mg. of iron in a liter, while cow's milk has barely one-third as much—really a negligible quantity. By these figures iron forms but 0.00007 per cent. of the ash of cow's milk, and 0.00015 per cent. of the ash of woman's milk.

#### SUMMARY

1. The use of large individual samples of milk for analyses has advantages not offered by such small ones as have been commonly employed. For a determination of the inorganic constituents large samples are indispensable.

2. In the colostrum period woman's milk has high protein and high ash with rather low fat; in the transition period the protein and ash are lower while the fat is higher; in the mature period (after one month) the composition of normal milk does not vary in any essential or constant way quite up to the end of lactation. The only striking feature of late milk is a decline in quantity, though there is noted a slight fall in all the solid constituents except the sugar.

3. Of the different constituents of milk the least variation both in individuals and in periods is seen in the sugar. The proportion of this is somewhat higher than the generally accepted 7 per cent.; 7.5 per cent. is nearer the correct figure.

4. The greatest individual variations are seen in the fat, though the period variations in fat are not marked.

5. The protein is highest in the colostrum period and falls to a little over half the proportion in mature milk, during which period it is seldom over 1.25 per cent.; of this about one-third is casein, and two-thirds lactalbumin.

6. The high ash of the colostrum period is chiefly due to the amount of  $\text{Na}_2\text{O}$  and  $\text{K}_2\text{O}$ . Of the salts which make up the ash, the greatest individual, as well as the greatest period, variations are seen in the  $\text{Na}_2\text{O}$ ; the least individual and period variations are seen in the  $\text{CaO}$ , the proportion of which is nearly constant throughout the period of lactation.

7. The largest constituent of the ash of woman's milk is  $\text{K}_2\text{O}$ ; this with the  $\text{CaO}$  together make up more than half the total ash.

8. Although in amount the total ash of cow's milk is about three and one-half times as great as that of woman's milk, the proportion of different salts which make up the ash is nearly the same, the only exceptions being that cow's milk has more  $P_2O_5$  and less iron.

We desire to express our thanks to those who have assisted us in obtaining specimens of milk for examination; especially to Dr. Herman Schwarz, Prof. J. Clifton Edgar, Dr. F. C. Freed and to the House Staff of the New York Foundling Hospital.

# STUDIES IN THE ADAPTATION OF AN ARTIFICIAL FOOD TO HUMAN MILK \*

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INTRODUCTION BY H. J. GERSTENBERGER

In 1910, the physiologist, Friedenthal<sup>1</sup> again picked up the threads which led to the ideal set up by the pediatricist Biedert a generation ago; namely, to the production of an artificial milk similar in all its important characteristics to the best food for the human infant, namely, breast milk. By not getting the results that it had expected from mixtures which took into consideration the quantities of protein, lactose, and fat in human milk, the pediatric world became discouraged and considered the production of an artificial human milk that would give good practical results a hopeless task. Friedenthal gathered courage for another attempt for the solution of this important and interesting problem from the fact that the salt content and the physical-chemical characteristics of human milk had been entirely neglected, and also from the conviction that these were important, if not the most important individual factors to be considered in the making of an artificial food that was to be similar to breast milk and which would give satisfactory results. Müller and Schloss,<sup>2, 4</sup> and Helbich<sup>3</sup> had also independently of Friedenthal begun with the attempt to come closer to the composition of breast milk. They received their stimulus from Finkelstein's theory of the injuriousness of the whey of cow's milk. Their first object, therefore, was to modify by reduction the deleterious

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\* For the apparatus, the materials and help used in making G-R milk, we are indebted to the Walker-Gordon Laboratory, Cleveland, Ohio.

\* Presented at the Annual Meeting of the American Pediatric Society, Lakewood, N. J., May 24, 1915.

1. Friedenthal, H.: Ueber die Eigenschaften künstlicher Milchsera und ueber die Herstellung eines künstlichen Menschenmilchersatzes, *Zentrallbl. f. Physiol.*, 1910, xxiv, 687.

2. Müller, Erich, and Schloss, Ernst: Die Versuche zur Anpassung der Kuhmilch an die Frauenmilch zu Zwecken der Säuglingsernährung, *Jahrb. f. Kinderh.*, 1914, lxxx, 42.

3. Helbich, H.: Die Bedeutung der Molkenreduktion für die Ernährung junger Säuglinge, *Jahrb. f. Kinderh.*, 1910, lxxi, 655.

4. Schloss, E.: Ueber Säuglingsernährung, Berlin, 1912, S. Karger.

why of cow's milk. They, however, encouraged by the favorable results that they had had in their institution with high fat milks, also attempted to simulate more accurately than heretofore the composition of breast milk. Schloss stated in his address at the Königsberger meeting of the Gesellschaft für Kinderheilkunde in 1910, that he and his co-workers were convinced that the road that they were following would ultimately lead to the solution of the problem of the production of an adequate artificial food. So while they had visions of accomplishments along this direction, Friedenthal<sup>1</sup> had already, from theoretical grounds, worked out a plan according to which a more complete adaptation of an artificial food to breast milk could be obtained. In his article Friedenthal states that artificial woman's milk ought to contain 0.7 per cent. casein, 0.8 per cent. albumin and globulin, 7 to 8 per cent. milk sugar,  $3\frac{1}{2}$  per cent. fat, ash, a freezing point of  $-0.56$ , degrees electrical conductivity of  $23 \times 10^{-4}$  at 18 degrees, neutral reaction (H Ion Content  $5 \times 10^{-8}$ ) besides traces of nuclein, lecithin and albuminoids, and have the proper energy content. Friedenthal further states in a later contribution (note 20) that the correlation of the salt components is of greater importance than is the total ash content.

Schloss<sup>2, 4</sup> then tried out Friedenthal's milk but did not get satisfactory results and, therefore, again modified this product. Schloss, in order to have more accurate data as to the ash composition of human and cow's milk, himself made analysis. The analyses on breast milk made by Schloss are of great value because he was the first to use samples of twenty-four hour quantities of breast milk for his determinations. In addition, he took samples of a mixed milk composed of full twenty-four hour specimens of eight women. The analyses that he got differed from those accepted up to that time. His further work, therefore, was based on the more dependable, analytical figures obtained by himself in this manner. Schloss,<sup>4</sup> however, felt that the poor results that he had obtained with Friedenthal's milk were due mainly to the lactose content, and he therefore replaced this with the preparation containing maltose and dextrin, and oftentimes in addition cornstarch. He also added a proprietary preparation of sodium caseinate to bring up the protein content.

By making these changes Schloss really left the road that leads to the complete adaptation of an artificial food to woman's milk, and, therefore, Friedenthal's milk, although based on less accurate analytical data, comes closer to the accomplishment of this ideal than does Schloss' milk.

Bahrtdt<sup>5</sup> reports favorably his experience with the feeding of this milk in eighty-one cases. He states that at least among the children

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5. Bahrtdt, H., Bamberg, Edelstein, Hornemann: Ernährungsversuche mit Friedenthalscher Milch, *Ztschr. f. Kinderh.*, Orig., 1914, x, 303

of the Kaiserin Augusta Victoria-Haus, Friedenthal's milk promises better results than those obtained with mixtures of simple dilutions with carbohydrate additions. Although the analytical and the metabolism work presented in his article has been seemingly justly criticized by Müller and Schloss,<sup>2</sup> this fact does not necessarily disprove the good clinical results obtained by Bahrtdt. It was the writer's impression when he in 1913 personally conversed with Bahrtdt regarding his results with Friedenthal's milk that this food did really give good results and did mean a distinct addition to our means. Both in the personal conversation and in the article which Bahrtdt published later, he emphasized the nearly universal presence of vomiting and marked spitting and of dyspeptic stools in most of the infants fed with this food.

This fact, together with the interesting and important experimental data obtained by Huldshinsky,<sup>6</sup> namely, (1) that the stomach of infants fed with human milk contains very small amounts of the low volatile fatty acids; (2) that the stomach of infants fed with cow's milk contains three to six times as much; (3) that the amount of the low volatile fatty acids found in the stomach of babies fed with cow's milk corresponds to the amount of fat in the milk; and (4) that the formation of these free low volatile fatty acids in the stomach of a healthy infant fed on cow's milk is caused by the splitting of the glycerids of these acids by a ferment, and that the type of the former low volatile fatty acids found in the stomach corresponds to the type existing in a preformed state in the milk fat, led me to believe that probably the qualitative differences between cow's milk fat and breast milk fat were to blame, in a large measure at least, for the excessive spitting, vomiting, and dyspeptic stools.

It is a recognized fact that cow's milk fat contains many more of the low volatile fatty acids than does breast milk fat (10 per cent. to 1.6 per cent. Langstein and Meyer<sup>7</sup>), and there are those—Bokai,<sup>8</sup> Bahrtdt,<sup>9</sup> Czerny,<sup>10</sup> and others—who believe that the low volatile fatty acids play an important part in the production of acute nutritional dis-

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6. Huldshinsky, K.: Untersuchungen über die Pathogenese der Verdauungsstörungen im Säuglingsalter; Mitteilung, V.: *Ztschr. f. Kinderh., Orig.*, 1912, III, 366.

7. Langstein-Meyer: *Säuglingsernährung und Säuglingsstoffwechsel*, Ed. 2 and 3, pp. 22, 23, 29 and 133.

8. Bokai, A.: Experimentelle Beiträge zur Kenntniss der Darmbewegungen. C. Ueber die Wirkung einiger Bestandteile der Fäces auf die Darmbewegungen, *Arch. f. exper. Path. u. Pharmakol.*, 1888, xxiv, 153.

9. Bahrtdt, H., and McLean, Stafford: Untersuchungen über die Pathogenese der Verdauungsstörungen im Säuglingsalter; VIII. Mitteilung, *Ztschr. f. Kinderh., Orig.*, 1914, xi, 143.

10. Czerny-Keller: *Des Kindes Ernährung Ernährungsstörungen und Ernährungstherapie*, Abt. 7, p. 137, Franz Deuticke, Wien, 1909.

turbances in infants. While Bahr<sup>11</sup> states that Huldshinsky's findings of the absence of an increase in the low volatile fatty acid content in the stomach of infants ill with acute nutritional disturbances speak against the importance of the low fatty acid content of infants' stomachs, on the other hand, he does believe that a disturbance of the motor and secretory powers of the stomach might alter conditions in the stomach and upper intestine in a manner that would permit the low fatty acids of the stomach contents to play an important etiologic rôle. It seemed plausible to the writer to imagine that if, for instance, the function of the pylorus could be disturbed in a manner that would permit larger quantities of food to enter the duodenum than it would under normal circumstances, that then the actual per cent. of low volatile fatty acids in the stomach contents at the time might be an important factor in the production of an acute nutritional disturbance and in the determining of the severity of the same, and that, therefore, the relatively large per cent. of low volatile fatty acids in cow's milk fat might be of decided etiologic importance. He therefore decided to attempt to obtain a fat, vegetable or animal, or a combination of such fats, that would give the same per cent. of the low volatile fatty acids as found in the fat of breast milk. In the first conference which I had, during December, 1913, with Dr. H. D. Haskins, Assistant Professor of Biological Chemistry at Western Reserve University, regarding this plan, the practical question of mixing such a fat with Friedenthal's milk was considered. It was immediately realized that the only hope lay in the use of an homogenizer, in which I had become interested a few years previously in an attempt at the Walker-Gordon Laboratory to make a very fine curd for casein milk. It was then learned that the Belle Vernon-Mapes Dairy Company was planning to put an homogenizer in the new plant which they were building, and it was therefore decided to wait with the practical work until the homogenizer had arrived, and in the meantime finish, if possible, our theoretical plans. In the literature I came across Arnold's<sup>12</sup> work, "*Ueber Frauenmilchfett*," in which he makes a statement that it is possible to make out of a mixture of 14 per cent. coconut oil and 86 per cent. lard, of the following characteristics:

	Cocoanut Oil	Lard
Refraction .....	35.1	47.7
Saponification number .....	259.0	197.5
Reichert-Meissl number.....	9.0	0.4
Iodin number .....	8.5	53.0
Polenske number .....	15.8	0.15

11. Bahr<sup>11</sup>, H., Edelstein, F., Hanssen, P., Welde, E. F.: Untersuchungen ueber die Pathogenese der Verdauungsstörungen im Säuglingsalter; X. Mitteilung, Ztschr. f. Kinderh., Orig., 1914, xi, 416.

12. Arnold, W.: Ueber Frauenmilchfett, Ztsch. f. Untersuch. d. Nahrungs- u. Genussmittel, 1912, xxiii, 433.



a fat that would give a refraction, saponification number, Reichert-Meissl number, iodine number, and Polenske number, very close to that of the fat of breast milk. It was decided, therefore, to use these data in the experimental and clinical work as soon as the homogenizer had arrived. While we were waiting, Niemann's<sup>12</sup> article on "Ueber die Möglichkeit einer Fettanreicherung der Säuglingsnahrung," appeared. He evidently had in mind the same goal as I, but had decided to reach it over another route, namely, over that of washed butter. Inasmuch as he claimed in his article to get an adequate removal of the low fatty acids from the butter by washing it with water, and also by vigorous stirring of a heated mixture an adequate and permanent emulsion of fat, together with Drs. Haskins and Ruh, I set myself at work to carry out Niemann's suggestion regarding the freeing of butter from the low volatile fatty acids with the idea of adding this fat to Friedenthal's milk. We hoped that by heating and vigorous stirring we were to accomplish the same permanent emulsification that Niemann<sup>12</sup> had obtained, with what results will be stated later.

The work of Funk<sup>14</sup> regarding vitamins, and his theory on the etiology of rickets, the work of Osborne and Mendel,<sup>15</sup> Peiser<sup>16</sup> and Bruning<sup>17</sup> on the growth value of the various food substances, especially fats, the work of Hess<sup>18</sup> on scurvy, the findings of Bahrdt,<sup>7</sup> Edelstein and Csonka<sup>19</sup> regarding the iron content of human and cow's

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13. Niemann, Albert: Ueber die Möglichkeit einer Fettanreicherung der Säuglingsnahrung, *Jahrb. f. Kinderh.*, 1914, lxxix, 274.

14. Funk, Casimir: The Nitrogenous Constituents of Lime-Juice, *Biochem. Jour.*, vii, 81; *Fortschritte der experimentellen Beriberiforschung in den Jahren 1911 bis 1913*, München. med. Wchnschr., 1913, ix, 1997; An Attempt to Estimate the Vitamine-Fraction in Milk, *Biochem. Jour.*, 1913, vii, 211; Studien ueber das Wachstum, Mitteilung 1. Das Wachstum auf vitaminhaltiger und vitaminfreier Nahrung, *Hoppe-Seylers Ztschr. f. physiol. Chem.*, 1913, lxxxviii, 352; Ueber die physiologische Bedeutung gewisser bisher unbekannter Nahrungsbestandteile der Vitamine, *Ergebn. d. Physiol.*, 1913, xiii, 124.

15. Osborne, Thos. B., and Mendel, Lafayette B.: Mendel, Lafayette V.: Viewpoints in the Study of Growth, *Biochem. Bull.*, 1914, iii; The Nutritive Significance of Different Kinds of Foodstuffs, *Med. Rec.*, New York, 1914, lxxxv, 737. Osborne, Thos. B., and Mendel, Lafayette B.: The Influence of Butter-Fat on Growth, *Jour. Biol. Chem.*, 1913, xvi, 423; The Influence of Codliver Oil and Some Other Fats on Growth, *Jour. Biol. Chem.*, 1914, xvii, 401; Feeding Experiments with Fat-Free Food Mixtures, *Jour. Biol. Chem.*, 1912, xii, 81; Further Observations on the Influence of Natural Fats Upon Growth, *Jour. Biol. Chem.*, 1915, xx, 379.

16. Peiser, J.: Ueber Fettaustausch in der Säuglingsernährung, *Berl. klin. Wchnschr.*, 1914, li, 1165.

17. Brüning, Hermann: Untersuchungen ueber das Wachstum von Tieren jenseits der Säuglingsperiode bei verschiedenartiger künstlicher Ernährung, *Jahrb. f. Kinderh.*, 1914, lxxix, 305.

18. Hess, Alfred F., and Fish, Mildred: Infantile Scurvy: The Blood, the Blood Vessels, and the Diet, *AM. JOUR. DIS. CHILD.*, 1914, viii, 385.

19. Edelstein, F., and Csonka, F. v.: Ueber den Eisengehalt der Kuhmilch, *Biochem. Ztschr.*, 1912, xxxviii, 14.

milk, the theories of Friedenthal<sup>20</sup> regarding the need of sufficient "*Bausteine der Kernstoffe*," are all of the greatest importance to the solution of the problem of a more perfect and complete adaptation of an artificial food to human breast milk, and must receive full consideration. While various mixtures have been prepared with the object of taking into account the work of some of the authors just mentioned, the present presentation aims to confine itself mainly to the analytical, bacteriologic, physical, mechanical, practical and few clinical data obtained in the work with the preparation of our so-called G-R milk No. 2, which represents nothing more or less than Friedenthal's milk in which butter fat has been replaced with another fat having about the same per cent. of low volatile fatty acids as breast milk has, and having in addition other characteristics more similar to breast milk fat than to cow milk's fat. Some analytical data regarding the fats of G-R milk Nos. 3, 4, and 5 will also be presented as well as the experience of the authors with butter washed according to Niemann.

#### PART I

##### *Homogenization*

*A. Homogenizer.*—The machine procured for us by the Walker-Gordon Laboratory was a Manton-Gaulin machine with a pressure capacity for 500 kilograms. Its liquid capacity was found by us to be about 200 c.c. The pressure used by us was 250 kilograms.

*B. Technic Carried Out in the Homogenization of Various Mixtures.*—(a) Fats—butter fat, lard, cocoanut oil, cocoa butter, codliver oil: The various fats were weighed out in sterile granite dishes. The dishes with the fats were put into a steam jacketed kettle of hot to boiling water until the contents became liquid. The pans containing the fat were then emptied and drained into a larger steam jacketed kettle into which all the other ingredients of the food had been mixed. The amount of fat remaining in the pans after thorough draining was so small as to be negligible.

(b) Sugar: The lactose was at first added in the form of a sugar solution of 19 to 21 per cent. Later on it was found more convenient and more accurate to simply weigh the lactose in the sterile granite pan and dump it into the common mixing kettle.

(c) Salts: The salts were accurately weighed in a glass receptacle. The contents of the receptacle were dumped into the mixing vat and the particles adhering to the inside of the dish rinsed out with distilled water. This amount, of course, was deducted from the batch of distilled water measured for the entire quantity.

(d) Skimmed milk: The amount of required skimmed milk was added to the mixture in cubic centimeters. To save time different granite pitchers were carefully marked for definite amounts.

(e) Water: The amount of required distilled water, less 200 c.c. for the capacity of the machine, was measured in cubic centimeters and added to the

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20. Friedenthal, H.: Ueber Säuglingsernährung nach physiologischen Grundsätzen mit Friedenthal'scher Kindermilch und Gemüsepulvern, Berl. klin. Wehnschr., 1914, li, 727.

mixture. To save time different granite pitchers were carefully marked for definite amounts.

(f) Quantity: The amount most frequently used by us for an individual batch was 30 liters.

(g) Mixing: 1. mixing before homogenization: Inasmuch as the largest steam jacketed kettle at our disposal could comfortably hold but 20 liters, the fat, salt, sugar, skimmed milk, and enough water to make about a total of 20 liters were put into the vat, stirred vigorously, and brought by steam heat to a temperature of 150 F. In order to avoid an excessive loss of the fat, which would occur if the mixture were allowed to go through the homogenizer undisturbed, it was necessary to keep up a constant stirring. Soon it was possible to develop a special technic in this respect that enabled a constant mixture of the fat with the other parts of the batch. At a time when nearly all of the 20 liters had passed through the homogenizer, the remaining water was poured into the vat and run through the machine.

Recently another larger receptacle has been used for mixing all of the milk and water at one time. Out of this receptacle the milk and water mixture is run in desired amounts into the steam jacketed kettle containing the sugar, the fat, and salts. The use of this extra receptacle has lessened the time and made the practical part of the work more simple.

2. Mixing after homogenization: From the above, it will be recognized that the first part of the mixture going through the homogenizer is much more concentrated than the second part. Therefore, it is essential that a mixture of all these parts be brought about before bottling. This was managed by pouring from one can to another.

Recently we have been pouring all of the homogenized milk into the same receptacle in which the water and skimmed milk had been mixed before homogenization. This also is more simple and saves time.

(h) Temperature: The temperature of the mixture is brought to 150 F. before it is allowed to go through the homogenizer. It is easy to keep the batch at this temperature by regulating the steam going through the kettle and the cold skimmed milk and water coming out of the large mixing receptacle. The temperature of the milk rises about 8 to 10 degrees in the process of homogenization. During the filling, bottling, capping, etc., it drops again to about 145 to 135, and it usually enters the ice box at this temperature.

(i) Bottling: From the large mixing vat the milk is run into a small enamel bottling machine and filled into bottles sterilized in an autoclave. The bottles are then capped with a simple cap and with a cover cap and placed in the ice box.

(j) Cleanliness: All of the bottles, dishes, and utensils are sterilized in the autoclave. The mixing vat is sterilized by allowing the water to boil in it. The homogenizer is cleansed and, in all probability, sterilized by running this boiling water through it just before the homogenization of the milk is to take place. This procedure also gives one the opportunity of testing the machine for any leaks.

No more than the usual precautions are taken with the packing, shipping, etc., of the fats, sugar, skimmed milk and water.

The hands of the individuals making the milk are simply cleaned with soap and water.

The authors are aware that Friedenthal requires that the skimmed milk be not heated. They have, however, felt that for their present work, at least, it would be better and safer practically to pasteurize the finished product. In all probability there will be no difficulty when the time comes to add at least a big part of the skimmed milk in a raw state to the finished product.

## PART II

*Butter Fat*

*A. Creamery Butter.*—(a) Cold water washing: Fresh, sweet creamery butter, in packed and in granular form, was vigorously and thoroughly rubbed and washed with some eight to ten changes of cold water. The acidity of the wash water was determined by the use of phenolphthalein and a tenth-normal sodium hydroxid solution. The amount of acids washed out was so small as to be insignificant.

(b) Hot water washing: Assuming that hot water might give better results, the butter was melted and the fat separated from the curd by passing through a cheesecloth. The filtered liquid was poured, together with hot distilled water, into a large bottle. The mixture was kept hot by placing the bottle in a water-bath. After thorough shaking the bottle was replaced in the water-bath and the fat allowed to separate from the wash water, which was then siphoned off for determination of its acidity. Four washings were carried out with each batch. Records of the amounts of tenth-normal sodium hydroxid required to neutralize the acids of the combined wash waters have been lost, but it can be stated that the amounts were so small as to be absolutely insignificant, and were, in all probability, due to the presence of a small amount of free acids and also caseinogen, which was being dissolved out. Burr and Weise<sup>21</sup> report that fresh butter fat always has a small amount of free fatty acids in amounts that require for 10 gm. of butter 0.6 to 1.4 c.c. tenth-normal sodium hydroxid solution. The best proof that the reduction in the low volatile fatty acid content of the butter was very insignificant is the finding for the same of a Reichert-Meissl number of 28, practically the same obtained in ordinary unwashed butter.

Grimmer<sup>22</sup> in his abstract of Niemann's article, criticizes Niemann's procedure and states that it is impossible to wash the low volatile fatty acids out of the butter because they are present in it in the form of glycerids, just as the higher acids are, and are, therefore, not free. In other words, Grimmer's statement corresponds with our findings.

(c) Alcohol washing: 263 gm. of clear butter fat were removed from one pound of fresh creamery butter, 255 c.c. of redistilled alcohol were added and the materials brought to boiling under thorough mixing. The mixture was then cooled to a low temperature and the alcoholic liquid decanted from the solid fat. The solid fat was then heated until the alcohol in it had evaporated. The residue weighed 252 gm. The Reichert-Meissl value of this residue fat was 4.0, and the iodine value 38.9. The addition of 10 gm. of sesame oil to 100 gm. to this alcohol washed fat gave an iodine value of 44.3. In other words, it is possible to remove the glycerids of the low volatile fatty acids from butter fat by washing with hot alcohol. The same plan has been carried out by Hunziker and Spitzer.<sup>23</sup>

(d) Emulsification according to Niemann: Both the cold water and the hot water washed butter fat were added to Friedenthal's milk in amounts to bring the fat content up to 4.5 per cent. The mixture was brought to the boiling point and was vigorously stirred, as directed by Niemann. The results were not the same as those obtained by Niemann, for the fat on standing and cooling rose to the surface. Niemann, however, used an entirely different mixture,

21. Burr, A., and Weise, H.: Ueber den Gehalt frischen Butterfettes an freien Fettsäuren und flüchtigen Fettsäuren, *Molkereizeitung*, Hildesheim, 1914, No. 16.

22. Grimmer, W.: Die Arbeiten auf dem Gebiete der Milchwissenschaft und Molkereipraxis im Jahre, 1914, I Semester, *Monatschr. f. Kinderh., Referate*, 1915, xiv, 81.

23. Hunziker, O. F., and Spitzer, G.: A Study of the Chemical Composition of Butterfat, and its Relation to the Composition of Butter, *Proc. Indiana Acad. Sc.*, xxv, 15.

which contained 50 gm. of mondamine (cornstarch) to each liter of milk, and this addition to his milk mixture was, in all probability, responsible for the difference in our results.

(c) Clinical data: Owing to the fact that the homogenizer was a very large machine used for the homogenization of large quantities of cream and was too large and unhandy for our work, and owing also to the climatic conditions that existed at that time—heat, August, 1914—only a few older, well babies were put on the milk simply to get a rough idea how the children would take it and react to it; that is, whether there would be an improvement over Bahrdt's<sup>5</sup> experiences or not. Only three older infants were put on Friedenthal's milk with cold water washed butter and two on Friedenthal's milk with hot water washed butter. Two of the former reacted with thin, yellow stools in increased numbers and one vomited severely. One of the latter reacted in the same manner. The mothers of these children were not enthusiastic about our giving their babies this "new milk" under such conditions, and we, therefore, because of this and the further reasons for limiting the number of babies in the first place, decided to discontinue our clinical investigations until the arrival of cooler weather and of the smaller homogenizer, which the Walker-Gordon Company was having made for our use. The impression that we gained from this very meager experience with Friedenthal's milk and water washed butter was that there was no improvement over the results obtained by Bahrdt with the regular Friedenthal's milk.

*B. Process Butter.*—Process butter was considered by us because of its cheapness and also because of the fact that it surely had ample chance to decompose and so have many of the low volatile fatty acids in a free state, which condition would enable us to remove the latter by washing the butter with water. The work with this material was soon dropped because of our inability to rid it from the very disagreeable odor.

### PART III

#### *Mixed Fats. Animal and Vegetable*

*A. General Statement.*—As stated in the introduction, our main object was to find a fat or combination of fats that would be more similar to breast milk fat than cow's milk fat, especially regarding the low fatty acid content, and to see whether a substitution of such a fat for the cow's milk fat in Friedenthal's milk might not improve this milk and represent a further step in the more complete adaptation of artificial food to human milk.

*B. Experimental Data.*—The accompanying table by Arnold<sup>12</sup> (Table 1) directed our attention to the use of lard and cocoanut oil:

TABLE 1

FROM ARNOLD'S WORK, "UEBER FRAUENMILCHFETT"

	Cocoanut Oil	Lard	Mixture	Woman's Milk Fat, I
Refraction .....	35.1	47.7	47.65	47.6
Saponification number.	259.0	197.5	206.1	206.08
Reichert-Meissl number	9.0	0.4	3.0	2.65
Iodin number.....	8.5	53.0	46.77	46.25
Polenske number.....	15.8	0.15	1.65	1.65

For many reasons it seemed worth while to try to make cod-liver oil a part of this fat combination. In order to make such a mixture more palatable cocoa butter was added. We, therefore, prepared four batches of fats in the following manner:

No. 2. Lard 86.00 per cent., cocoanut oil 14 per cent.

No. 3. Lard 74.88 per cent., cocoanut oil 14 per cent., codliver oil 11.11 per cent.

No. 4. Lard 63.78 per cent., cocoanut oil 14 per cent., codliver oil 11.11 per cent., cocoa butter 11.11 per cent.

No. 5. Lard 74.88 per cent., cocoanut oil 14 per cent., cocoa butter 11.11 per cent.

It was our intention to use all four of these, but for practical reasons, after having found out that infants would take any one of them, we decided to limit our experiences for the beginning to G-R milk No. 2.

Table 2 gives first, the character numbers of the individual fats; second, the character numbers of the fats of G-R milk Nos. 2, 3, 4, and 5, obtained by calculation on the basis of the character numbers actually found for the individual fats (the individual fats were mixed by heating at 60°); third, the character numbers of the fats mixed in the same proportion as they were mixed in the milk; fourth, the character numbers for the mixture of lard and cocoanut oil in the proportion as they were used in G-R milk No. 2, and heated for the same period of time as required to extract the fat from G-R milk No. 2; and fifth, the character numbers of the fat extracted from G-R milk No. 2.

TABLE 2.—DATA CONCERNING VARIOUS FATS USED

	Reichert-Meissl	Polenske	Iodin	Saponification
Lard .....	0.08	0.49	63.07	195.5
Cocoanut oil .....	6.436	13.69	8.836	259.5
Cocoa butter .....	0.34	0.30	36.35	196.4
Codliver oil .....	0.27	0.315	170.0	189.9
<i>Mixed fats:</i>				
(Same proportions)				
As Milk II (calculated) .	0.9698	2.337	55.45	204.5
As Milk II found .....	1.638	1.231	55.46	206.8
As Milk II found* .....	2.524	1.22	.....	.....
Fat from Milk II .....	2.72	1.2	55.0	206.0
(Same proportions)				
As Milk III (calculated) .	0.9914	2.318	66.24	203.8
As Milk III found .....	2.09	1.288	67.5	205.1
(Same proportions)				
As Milk IV (calculated) .	1.188	2.297	63.14	204.0
As Milk IV found .....	2.127	1.498	64.49	205.4
(Same proportions)				
As Milk V (calculated) .	0.8128	2.318	52.52	204.6
As Milk V found .....	1.971	1.301	52.75	206.3

\* Fats in same proportion as in Milk II heated with ether for same period of time as required to extract fat from milk.

Table 2 reveals the fact that it is possible to calculate the iodine and the saponification values of mixtures of fats before or after homogenization in milk, from a consideration of these values in the individual fats. The data with equal clearness show that the Reichert-Meissl and Polenske numbers may not be so calculated, but that the mixing of the fats produces a change in the relative amounts of soluble and insoluble fatty acids that will volatilize with steam in the time required for the determination. It is noteworthy that the total amount of the volatile fatty acids is not greatly changed, for the sum of Reichert-Meissl and Polenske numbers as found is in each case approximately the same as the sum of the calculated values. This variation is not now understood and further work will be done to determine the cause of the change in value.

The slight increase of 0.2 in the Reichert-Meissl number of the fat from G-R milk No. 2 over the mixture of the same fats in the same proportions and heated for the same period of time as required to extract the fat from G-R milk, is probably due to the 0.4 per cent. of butter fat present in the skimmed milk, as can be seen from Table 5.

By comparing the character numbers as given in Table 2 for G-R milk No. 2 with Arnold's figures for his mixture and for his woman's milk fat No. 1, it will be seen that the Reichert-Meissl and saponification numbers are nearly identical; that there is a slight difference between the Polenske numbers, and a decided difference between the iodine numbers. The difference between the iodine numbers is due to the high iodine value of the batch of lard used in our work (G-R milk, lard 63.07; Arnold, lard 53.0). By rearranging the mixture we could have procured an iodine value for the G-R milk fat which would have been closer to Arnold's figures for woman's milk fat, but by doing so we would have changed the Reichert-Meissl and the saponification numbers; but as the Reichert-Meissl value seems of first importance to us, we decided to continue to use this mixture without any further change, and it is, of course, probable that a fair increase in the iodine number above that found in woman's milk fat is of no great importance.

The following figures given by Arnold<sup>12</sup> for his analysis of another woman's milk fat (*Frauenmilchfett No. 2*),

Refraction .....	48.75
Saponification .....	205.0
Reichert-Meissl .....	1.5
Iodine .....	45.65
Polenske .....	1.45

show, as one, of course, would expect, that fat from milk coming from different women will show variances in the character numbers of their respective fats.

Merkel<sup>24</sup> reports the following as character numbers of a butter made from the cream of a four-day quantity of milk from a wetnurse:

Saponification number .....	209.3
Reichert-Meissl number .....	1.5
Polenske number .....	2.2
Iodine number .....	46.8
Refraction at 40° .....	46.3

Table 3 shows that by making use of tallow—which one might imagine from Osborne and Mendel's<sup>15</sup> work, might even have an added value over lard—in the fat mixture, a greater resemblance as regards iodine numbers can be obtained.

24. Merkel, Eduard: Zur Kenntnis des Frauenmilchfettes, Pharm. Zentralhalle, 1912, liii, 495.

TABLE 3.—CHARACTER NUMBERS OF INDIVIDUAL FATS

	Saponification	Reichert-Meissl	Iodin
Lard .....	195.29	0.08	63.1
Tallow .....	196.6	0.5	41.4
Cocoanut oil .....	259.5	6.43	8.8
Cocoa butter ....	196.4	0.34	36.3
Codliver oil .....	189.9	0.27	170.0

## MIXTURE WITHOUT CODLIVER OIL

	Per Cent.	Saponification	Reichert-Meissl	Iodin
Lard .....	50	205.48	1.07	47.36
Tallow .....	35			
Cocoanut oil .....	15			

## MIXTURE WITH CODLIVER OIL

	Per Cent.	Saponification	Reichert-Meissl	Iodin
Tallow .....	45	205.46	1.285	45.17
Lard .....	15			
Cocoanut oil .....	15			
Cocoa butter .....	20			
Codliver oil .....	5			

Table 4 shows the materials used for a typical batch of G-R milk No. 2. The table is analyzed to show the origin of the various contributing substances:

TABLE 4.—MATERIALS FOR G-R MILK No. 2

	Total gm.	Water	Salt	Per Cent. Protein	Fat	Lactose
Skimmed milk ...	9,890	27.23	0.2184	0.96	0.132	1.463
Water .....	19,800	60.07	.....	.....	.....	.....
KCl .....	27	.....	0.0819	.....	.....	.....
K <sub>2</sub> HPO <sub>4</sub> .....	13.5	.....	0.0409	.....	.....	.....
KH <sub>2</sub> PO <sub>4</sub> .....	13.5	.....	0.0409	.....	.....	.....
Lard .....	1,274.5	.....	.....	.....	3.867	.....
Cocoanut oil ....	207.5	.....	.....	.....	0.629	.....
Lactose .....	1,740	0.0425	.....	.....	.....	5.235
Totals .....	32,966	87.34	0.382	0.96	4.628	6.698

The distribution of the substances from the skimmed milk shown in Table 4 is based on the analysis of the milk used, shown in Table 5.

TABLE 5.—DISTRIBUTION OF SUBSTANCES FROM SKIMMED MILK  
SKIMMED MILK JUNE 18

Water .....	90.51
Ash .....	0.728
Protein .....	3.2
Fat .....	0.44
Lactose .....	4.87

The composition and characters of the G-R milk No. 2 prepared from the batch given in Table 4, as determined by analysis, are summarized in Table 6.

TABLE 6.—COMPOSITION AND CHARACTER OF G-R MILK No. 2  
ANALYSIS

Water .....	87.21
Ash .....	0.378
Protein .....	0.93
Fat .....	4.617
Lactose .....	6.65



General characters: Specific gravity 15.5 °, 1.032; specific conductivity 20 °,  $3.41 \times 10^{-3}$  recip. ohms; freezing point depression 0.618°; caloric value per kg., 739.6 cal.

Characteristics of fat content: Size fat globules, 0.2-1 micron; brownian movement vigorous; Reichert-Meissl value, 2.72; Polenske number, 1.2; iodine number, 55.0; saponification number, 206.0.

That the milk maintained the same general composition may be judged from the accompanying analyses made at different periods (Table 7).

TABLE 7.—ANALYSIS OF G-R MILK No. 2, AT DIFFERENT PERIODS

	May 18	May 20	June 5	June 18
Water .....	86.8	87.14	87.44	87.21
Ash .....	0.43	0.37	0.37	0.378
Protein .....	1.1	0.97	0.91	0.93
Fat .....	4.52	4.58	4.6	4.617
Lactose .....	7.07	6.63	6.51	6.65

The somewhat low protein and lactose content is due, in a part at least, to the fact that the milk was added as grams instead of c.c.

TABLE 8.—BACTERIAL COUNTS FOR SKIMMED AND FINISHED MILKS

Date		Count	Skim, Count
May 6	No. 2 II	Sterile	.....
May 6	No. 2 III	Sterile	.....
May 6	No. 2 IV	Sterile	.....
May 6	No. 2 V	Sterile	.....
May 12	No. 2 II	3,100	.....
May 12	No. 2 III	5,000	.....
May 12	No. 2 IV	16,100	9,850
May 19	No. 2	1,850	.....
May 20	No. 2	4,500	55,300 *
May 21	No. 2	6,000	91,000 *
May 22	No. 2	Sterile	11,300 *
May 24	No. 2	Sterile	19,700 *
May 25	No. 2	Sterile	.....
May 26	No. 2	Sterile	39,000 *
May 27	No. 2	Sterile	5,500 *
May 31	No. 2	Sterile	.....
May 29	No. 2	4,900	.....
June 2	No. 2	1,000	2,400
June 4	No. 2	Sterile	7,200
June 5	No. 2	300	8,400
June 7	No. 2	Sterile	157,200
June 9	No. 2	Sterile	6,800
June 11	No. 2	1,700	4,500
June 12	No. 2	9,000	2,000
June 14	No. 2	3,100	42,000
June 16	No. 2	Sterile	70,000
June 19	No. 2	200	3,200
June 20	No. 2	700	400
June 25	No. 2	200	300
June 26	No. 2	300	2,700

\* Not certified skim.

Table 8 gives the bacteriological counts for the skimmed milk and for the finished milks, and shows on the whole very low bacterial counts for the prepared milk. These excellent results are, in all proba-

bility, due to the fact that, unknowingly, practically the same technic and conditions were established by us as advocated by Ayers and Johnson.<sup>25</sup>

*Analytical Methods.*—Water, Ash, Protein: The methods used for determining water, ash and protein are those of the A. O. A. C. described in Bulletin 107 of the Department of Agriculture.

Fat: The usual methods for fat extraction and estimation are completely unreliable with homogenized milk of this type. When the Babcock centrifugal method is used a definite separation of fatty from acid layer cannot be obtained. Various determinations were made by the Adams paper coil method, and the following figures obtained on milk that by more accurate analysis was shown to contain 4.5 per cent. of fat: 3.75, 3.69, 3.34, 2.24 per cent. A modification of the Werner-Schmidt acid method yielded fairly close results, but very great difficulty was experienced in securing a separation of the acid and ether layers. The Roesse-Gottlieb process was then employed, and it was found that excellent results can be obtained when low-boiling petroleum ether (35 C.) is used, and the second and third extractions accomplished by inversion, without shaking, of the mixture. The above recorded analyses substantiate the accuracy of this method.

Method of Fat Extraction from Milk: 150 c.c. of milk were diluted with 250 c.c. water, and 9 c.c. of 1 per cent. sulphuric acid added, with constant stirring. A cylindrical cup made from fat-free filter paper was fitted closely into a Buchner funnel and after moistening the paper the acidified mixture was filtered. After normal filtering had ceased, the filtrate was discarded and suction applied until most of the water was removed. This final filtrate was shaken with ether, and the ether subsequently used for the extraction of the fat from the precipitate. The filter paper with precipitate was transferred to a mortar and ground with about 20 gm. anhydrous sodium sulphate, when a dry, somewhat waxy porous powder resulted. This powder was placed in a Soxhlet apparatus, where extraction was complete in two hours. The ether was then driven off, or in some cases the ether solution was transferred by pipet to the vessel in which a determination was to be made.

Reichert-Meissl Value: Leffmann and Beam's saponification method was used, and the distillation continued thirty minutes.

Polenske Number: Glycerol saponification was used, and the condenser tubes washed three times with water, then three times with alcohol.

Iodin Number: The Wjis method was used.

Saponification Number: One gm. of the fat was saponified with 5 per cent. potassium hydroxid in specially purified alcohol. It is of importance that the blank determination be heated on the water bath for the same period of time as the regular determinations.

Size of Fat Globules: The value of 0.2 to 1 microns was roughly approximated by the use of Thoma's hemacytometer. The fat globules exhibit remarkable uniformity of size, and all show vigorous brownian movement.

Lactose: The solid lactose used was examined both polarimetrically and by reduction, and found to be 99.2 per cent.,  $C_{12}H_{22}O_{11} \cdot H_2O$ . Lactose in milk was determined in each case by the polarimeter, using acid mercuric nitrate for precipitation, and estimating the solids by the method of double dilution. To check the polarimetric method, the milk analyzed on June 18 was determined also by the reduction method, using Soxhlet's modification of Fehling's solution, weighing the copper as cupric oxid, and calculating lactose from the

25. Ayers, S. H., and Johnson, W. T., Jr.: Pasteurization in Bottles and the Process of Bottling Hot Pasteurized Milk, Jour. Infect. Dis., 1914, xiv, 217.

Soxhlet-Wein tables. The results show the absence of any substances in the milk that would vitiate the accuracy of the polarimetric method.

Per cent. lactose by polariscope .....6.51  
Per cent. lactose by reduction .....6.537

Specific Gravity: Quevenne's lactodensimeter was used at 15.5 C.

Conductivity: Conductivity was measured by the Kohlrausch method, using a cell with electrodes about 1 cm. apart and 2.5 cm. in diameter.

Depression of Freezing Point.—The determination was made by the usual method. It is highly important that the temperature of the freezing mixture be not lower than about  $-1.5^{\circ}\text{C}$ . as the concentration of the solution by the settling out of ice changes the f. p. significantly.

Calorimetry: To determine the heating value, 2 c.c. of milk were accurately weighed in a small combustion cup. This was placed in a desiccator equipped with shelves holding dishes filled with calcium chlorid. Evacuation was accomplished by a water pump, and in twenty-four hours the material had dried and showed no evidence of loss by spattering. The dried milk was then burned in a Parr bomb with 20 atmospheres oxygen pressure. The calculation of heating value from the analysis of milk reported in Table 7 (June 18) closely agrees with the direct calorimetric determination.

#### CALCULATION FROM ANALYSIS

Protein	0.93	$\times$ 5.85	5.44 C.
Fat	4.617	$\times$ 9.1	42.02 C.
Lactose	6.65	$\times$ 3.96	26.33 C.

73.79 C. per 100 gm. milk

Obtained from calorimeter 73.96 C. per 100 gm. milk

*C. Clinical Data.*—(a) Vomiting: The clinical experience until now has not been sufficient to be considered worthy of report. It is hoped at a later time to present the clinical results. A statement, however, can be made regarding the degree of vomiting and dyspeptic stools met with so frequently by Bahr<sup>26</sup> in his patients fed with Friedenthal's milk prepared with unchanged cow's fat. Of a list of twenty babies, from 1 week to 7 months of age, there was spitting up or slight vomiting in five. In two of these this has disappeared; in a third, the vomiting continues once a day; and in the other two there still exists a slight vomiting. Two other children showed marked vomiting before they were put on the food; the one gradually improved while on the milk, and now does not vomit at all, and the other is a case of pylorospasm which continues to vomit, but which has begun to gain in weight since it has been getting the food.

(b) Stools: Of the twenty children only two showed dyspeptic stools. Two were constipated and passed rather firm, somewhat formed, fatty soap stools. The remainder had what we termed normal stools. These varied in color from a lemon-yellow to an orange-yellow, were of a lard-like, pasty consistency, and contained, in most instances, smaller or larger masses of soft, fatty soaps. Many of the stools changed from a yellow to an olive-green in the diaper.

These few data suffice to prove that the vomiting has been decidedly less and the stools decidedly more normal in our children than they were in Bahr<sup>26</sup>'s, and we believe that this is due to the removal of the low volatile fatty acids. Whether the fact that the milk was homogenized has anything to do with these better results is impossible to say at the present time. Birk, according to Grulee,<sup>26</sup> could find no improve-

26. Grulee, Clifford G.: *Infant Feeding*, W. B. Saunders Co., 1912.

ment in the children by homogenizing their foods. On the other hand, Lavalie<sup>27</sup> believes that the homogenization greatly enhances the digestibility of a milk because it offers to the digestive ferments a much larger action surface, and because it causes, by reason of the marked brownian movement, the formation of currents, which are responsible for an active mixing of ferments and foods. Inasmuch as the fat in human milk does not exist in such a fine emulsion as the fat of homogenized milk, it can at least be assumed that a finer division than is present in human milk is not necessary; on the other hand, there is, at present, no reason to believe that any harm is done to the fat or any other constituent of the milk by homogenization, excepting, of course, the effect of the raised temperature on some of the constituents of skimmed milk; and it may be found that homogenization is of greater value in the production of artificial human milk than the mere mixing for which it has been used by us.

(c) Weight: The following figures are given to show that normal or slightly below normal infants made good gains in weight. Eighteen infants, from 1 week to 7 months of age, for a total period of seventy-three weeks, made a total gain of 10,630 gm., or an average of 145 + gm. per week.

*D. Economical Data.*—Friedenthal's milk made up with a mixture of fats like lard, tallow, cocoa butter, cocoanut oil, cod-liver oil, olive oil, cottonseed oil, sesame oil, and the like, can be produced at a price decidedly lower than when butter freed from a large per cent. of its low fatty acid glycerids is used. The cost of the fat per liter of various combinations with various fats, is as follows:

For a mixture of tallow 40 per cent., lard 10 per cent., cocoanut oil 20 per cent., cocoanut butter 20 per cent., codliver oil 10 per cent. ....	1.30 cents
G-R Milk No. 2 .....	1.43 cents
G-R Milk No. 3 .....	1.60 cents
G-R Milk No. 5 .....	1.70 cents
G-R Milk No. 4 .....	1.80 cents
Friedenthal's milk with cow's butter fat, without considering the cost of washing the butter with alcohol.....	3.70 cents

While the production cost of a milk for infants is not of the first importance, yet it is, nevertheless, true that there are many families who cannot get for their infants what they should have simply because of the price, and, therefore, if an adequate food can be prepared at a low cost it is an advantage that is important when it is desired that all families whose infants require it should get it. It is also interesting to think of the economy that would result in a general way by the reduction in the use of the more expensive butter and the increase in the use of fats that are distinctly cheaper.

27. Lavalie, P.: Le mouvement brownien dans le lait homogeneise, Clin. infant., 1913, xi, 490.

## SUMMARY

1. By mixing varying proportions of different animal and vegetable fats, it is possible to get a fat that in its Reichert-Meissl number (small per cent. of low volatile fatty acid glycerids), saponification number, iodine number, and other characters, is nearly identical with the fat of human milk, as has previously been shown by Arnold.
2. By replacing in an artificial milk cow's-milk fat with the fat of the above description in an emulsified state (homogenized), a distinct step in advance towards the more complete adaptation of an artificial food to breast milk is made.
3. It is also possible to take into consideration the "growth factors," "vitamine factors," and the like, in choosing the individual fats for an acceptable mixture. This represents a further step in the more complete adaptation of an artificial milk to human milk.
4. The homogenizer represents the important means by which the mixing and emulsification of the fat in the artificial milk is possible. The homogenizer also changes the physical condition of the fat (smaller globules, brownian movement), which may be of advantage.
5. The meager clinical data suffice to show that the infants fed with Friedenthal's milk in which the cow's-milk fat has been replaced by a fat with a low volatile fatty acid glycerid content, similar to that of human milk fat, vomit less and have more normal stools than the children reported by Bahrdrf, and fed with Friedenthal's milk containing unchanged cow's-milk fat.
6. Washing butter with cold or hot water does not remove the low volatile fatty acids from butter, except in an insignificant degree.
7. Washing butter with hot alcohol does remove the low fatty acid glycerids to a decided degree.
8. The manufacture of a food like G-R milk can be arranged to give a very low bacteriologic count.
9. The production of milk like G-R milk can be made at a reasonable cost.

## EXTENSIVE PURPURIC ERUPTIONS IN EPIDEMIC MENINGITIS \*

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Since epidemic meningitis was first described as "spotted fever" a great deal of just criticism has been directed against the term. Even the earliest writers admit that skin manifestations occur in a comparatively small percentage of the cases—too small, indeed, to justify the use of the title.

In his treatise on "A Malignant Epidemic Commonly Called Spotted Fever," North<sup>1</sup> draws attention to the fact that in the 1806-1807 epidemic in Massachusetts, skin eruptions were very common, while in the later epidemic of 1808-1809 they were almost never observed. "The size of the lesions varied from the head of a pin to a six cent piece and the distribution was more commonly on the face, neck and extremities." He believed that the color of the rash was a guide in prognosis; that is, the darker the shade the more hopeless the outcome.

In the Ireland epidemic in 1867, nearly every case showed skin manifestations. Gordon<sup>2</sup> reports several such cases and gives a very accurate description of the various forms of eruption.

Frew,<sup>3</sup> in 1884, describes seven cases during an epidemic in Scotland, three showing hemorrhagic eruptions; of these three, only one was purpuric. He believed, however, that there were numerous patients showing no eruption who recovered, and these he was not sure were the same disease.

In the Massachusetts epidemic in 1866, Webber<sup>4</sup> reports that 33 per cent. of the cases showed petechiae; only a few, however, were purpuric. Here also the color of the rash was considered to be an aid in prognosis.

This is in striking contrast to the epidemic in the same state in 1898, during which, according to the investigation by Councilman, Mallory and Wright<sup>5</sup> only eleven cases out of 111 showed eruption of any kind, and in only one was there a true extravasation into the skin.

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\* Submitted for publication July 21, 1915.

1. North, Elisha: A Treatise on a Malignant Epidemic Commonly Called Spotted Fever, T. and F. Swords, New York, 1811.

2. Gordon: Dublin Quart. Jour. Med. Sc., 1867, xliii, 408.

3. Frew, William: Glasgow Med. Jour., 1884, xxii, 21.

4. Webber, S. G.: Boston Med. and Surg. Jour., 1866, lxxv, No. 2, p. 29.

5. Councilman, Mallory and Wright: Report of State Board of Health of Massachusetts, Boston, 1898.

In a series of fifty cases occurring in New York city reported by Conner<sup>6</sup> in 1905, only 5 per cent. showed any eruption, and in a more recent outbreak in Texas, which was so thoroughly investigated by Sophian,<sup>7</sup> hemorrhagic eruptions were uncommon and true purpura extremely rare, being found in less than 1 per cent. of the cases.

These reports suggest that in the early history of the disease, skin eruptions were more frequent than have been observed recently. This is probably due to the fact that other forms of the disease were not recognized as they are today.

The two following cases are reported as examples of very unusual skin lesions in epidemic meningitis:

#### REPORT OF CASES

CASE 1.—F. H., aged two years, was admitted to the Babies' Hospital, Feb. 6, 1914, at 10 a. m.



Fig. 1.—Taken on the fourth day of the disease, showing eruption on buttocks and lower extremities, Case 1.

*History.*—There was no family history of hemophilia or any hemorrhagic disease and the child himself had never been sick before. The patient was well up to twenty-four hours before admission, when he seemed listless, appeared feverish and refused food. The only medication the child had received was twelve tablets of calomel, size unknown. At 11 p. m. the same day he seemed better and fell asleep. Two hours later the child awakened screaming and the mother then observed that the face was covered with a black eruption. On removing the bedclothes the eruption was discovered also over the extremities. This, she declared, had not increased up to the time of admission to the hospital. There had been no vomiting, no convulsions, and only slight fever. Stools were green and loose, but not tarry, and the urine was normal in color.

*Examination.*—On examination was found a well developed and nourished child, evidently severely ill, in a condition of semistupor, with marked pros-

6. Conner, L. H.: Med. News, 1899, lxxiv, 685.

7. Sophian, Abraham: Epidemic Cerebrospinal Meningitis, C. V. Mosby & Co., St. Louis, 1913.

tration. Did not respond to stimuli such as noises; was apparently deaf and blind; periods of drowsiness alternated with periods of restlessness and screaming. The child was extremely hyperesthetic when handled and was particularly so when the legs were moved. No opisthotonos was present but the neck was slightly stiff; knee jerks exaggerated; Kernig's sign, not elicited; pupils equal and reacted normally; no strabismus or conjunctivitis; tache cérébrale present. Respirations rapid but regular; examination of the lungs revealed nothing abnormal. Heart sounds were rapid and slightly feeble; the pulse small and thready, but regular; spleen not enlarged; slight general enlargement of superficial lymphatic glands in cervical, axillary, inguinal and epitrochlear regions; the nodes were soft, small and discrete.

Large blotches of purpura were found on the face, extremities and buttocks interspersed with petechiae of varying sizes. The intervening skin was blanched white and the combination presented an appearance which was ghastly; the child looked as though splashed with a quantity of black ink. The eruption was to some extent symmetrical in that it involved both sides of the



Fig. 2.—Taken on the fourth day of the disease, showing eruption on face and outer side of thighs, Case 1. Note the absence of lesions on the trunk.

face, both shoulders, the extensor surfaces of the arms, the buttocks and outside of the legs. The largest areas were found on the face, on the elbows, buttocks and thighs, one on the right thigh measuring 6 inches in length. The distribution did not appear to correspond to any particular nerve or vascular supply, but the fact that it was extensive over the elbows and buttocks suggested a possible traumatic etiology. The trunk, except for a few small petechiae, remained clear. The conjunctivae and the mucous membrane of the mouth and throat showed no eruption. The center of the larger patches was purple in color, the periphery was reddish brown, and surrounding this was a zone of hyperemia. There was a distinct elevation above the normal skin level. In some cases this subcutaneous infiltration seemed to correspond with the edge of the purpuric patch but this was not invariable, as the induration could be felt under normal skin in the immediate neighborhood of the larger hemorrhages. The areas of purpura seemed acutely tender and the skin of the whole body was hyperesthetic. The photographs shown in Figures 1 and 2 were taken on February 8 and give an idea of the widespread distribu-



tion of the eruption; Figure 2 shows very well the absence of the lesions on the trunk.

*Subsequent Course.*—The eruption did not spread during the day, but the temperature which on admission had been only 100 F., rose abruptly to 102.8 and the child vomited twice very forcibly. The leukocytes were 40,000 per c.mm. with 75 per cent. polymorphonuclears; hemoglobin 80 per cent.; platelets in moderate numbers found in the stained smear; coagulation time of the blood (specimen taken from vein and Duke's instrument used) was forty-five minutes; bleeding time, two and one-half minutes. Macroscopic, microscopic and chemical tests failed to show blood in either urine or feces. A slight internal strabismus of left eye developed during the day; ophthalmoscopic examination showed no papilledema and no retinal hemorrhages. Ears normal. Cultures were taken from the blood and from the purpuric patches. Lumbar puncture was performed and 20 c.c. of blood-tinged fluid was obtained which was cultured in various mediums.



Fig. 3.—Taken on the twelfth day of the disease, Case 1, showing the disappearance of many of the smaller lesions. The commencing separation of the gangrenous tissue is easily discernible at the margin of the larger areas.

The following day the patient was much less irritable and the screaming attacks less frequent. The muscles of the neck and back were more rigid; Kernig's sign absent. Leukocytes 22,000 per c.mm. with 78 per cent. polymorphonuclears; temperature ranging between 101 and 104. Coagulation time of the blood had dropped to twenty minutes; the eruption had not spread or changed in appearance. A second lumbar puncture gave 25 c.c. of turbid fluid, which was removed under increased pressure and showed on examination 4,000 cells per c.mm., of which 92 per cent. were of the polymorphonuclear variety. A direct smear of the fluid showed a very few intracellular and extracellular gram-negative diplococci; 20 c.c. antimeningitis serum were injected intraspinally.

The progress of the case from this point need not be given in detail. The child received intraspinal injections of the serum every day for three days, the size of the injection being controlled by the fluctuations in blood pressure. The cerebrospinal fluid became gradually less turbid; the cell count dropped to 350 per c.mm. on the sixth day of the disease and to 86 per c.mm. on the ninth day.

The leukocytes were estimated every day and ranged between 16,000 per c.mm. and 20,000 per c.mm. with a gradual drop in the polymorphonuclear percentage. The blood culture taken on February 6 showed in thirty-six hours a growth of meningococci; the organisms could not, however, be demonstrated in the culture taken on the following day. Spinal fluid cultures showed a faint growth of the same organism. Cultures from the purpuric patches remained sterile four days.

The mental condition of the child gradually improved, the vomiting ceased and the rigidity of the neck diminished. A transient right facial paralysis was noticed on February 9, which disappeared on the following day. The temperature after the eighth day of the disease ranged between 100 and 101 F. until the termination of the case.

The course of the eruption was so unusual as to deserve a more detailed description.

The rash on the fifth day of the disease showed a gradual change in color, the center of the larger areas became paler and the outside rim took on a rose-colored tint. On the sixth day one or two of the larger patches showed a central area, grayish-black in color, which had a consistency like cardboard. On the ninth day the smaller purpuric patches began to desquamate, leaving a depressed pigmented scar. The petechiae had also disappeared, leaving only a brown pigmentation. Two days later sloughing commenced at the margin in some places extending down to the muscle. The child's breath became very foul due to a separation which had commenced at the left margin of the ecchymosis on the nose. The necrosis penetrated to the nasal passages and through the sinus there was a profuse discharge of fetid mucopus, which was of a very foul and typically gangrenous odor. The photograph shown in Figure 3 was taken February 16 and illustrates the commencing slough at the upper margin of the lesion on the right thigh and hip. Comparison of Figures 1 and 3 shows the disappearance of the petechiae and smaller purpuric spots.

The necrosis continued until the gangrenous tissue had in some localities completely sloughed out leaving a large ulceration lined with unhealthy granulations. The entire tip of the nose became necrotic on the fifteenth day and was removed, exposing the nasal bones. The character of the lesions at this period bore a striking similarity to the extensive symmetrical gangrene seen in severe cases of Raynaud's disease.

The child's condition became progressively worse, the symptom complex being one of general sepsis. The temperature rose to 106.5 on February 22, the seventeenth day of the disease, and the child died the same day. Repeated convulsions occurred during the twenty-four hours previous to death; an exacerbation of the meningitis was suspected, but the cerebrospinal fluid on February 20 was found to be normal.

*Necropsy.*—An autopsy was performed on February 22 by Dr. Wollstein. With the exception of a superficial strip of bronchopneumonia along the posterior border of the right lower lobe, and a small hemorrhage on one cusp of the aortic valve, the thoracic and abdominal organs were normal. The pia mater at the base of the brain was turbid, but there was no exudate; the vessels of the pia everywhere were congested, most markedly so over the left cortical surface. The ventricles were not distended and contained a small amount of very slightly turbid fluid; the brain substance was congested. There was congestion of the pia mater along the entire length of the spinal cord but no sign of exudate. In short, the findings were those of a recovered case of epidemic meningitis.

CASE 2.—M. O., female, aged 15 months, was admitted to Babies' Hospital, June 11, 1915.

*History.*—A previously healthy child except for an attack of pneumonia in January, 1915, and measles in April, 1915; both diseases terminated without complication after running a perfectly normal course.

The mother's story was that on June 8 the child became abruptly ill with vomiting and fever. About eighteen hours later a rash suddenly appeared on the face and extremities; the mother declared she "could watch the spots coming out." The vomiting continued up to admission and the stools were loose and dark green in color. The infant had been listless, but there had been no convulsions.

*Examination.*—Examination revealed abnormalities only in the nervous and cutaneous systems. The child was slightly apathetic, irritable when handled and markedly hyperesthetic; acutely ill but not prostrated. Pulse and respirations regular. Very slight spasm on attempted flexion of the head on the chest; Kernig's sign absent; patellar reflexes, not exaggerated; tache cérébrale marked; ocular movements normal.



Fig. 4.—Taken on the eighth day of the disease, Case 2, showing eruption over outer surface of legs and thighs.

Scattered over the face, the upper and lower extremities and the buttocks was a hemorrhagic eruption. The majority of the lesions were purpuric, only a few petechiae being present. The spots were of various sizes and shapes, the largest being 13 mm. in length. On the extremities the lesions were found more commonly on the extensor surfaces. The trunk except for a few small spots over the scapular region was clear. The lesions were discrete and the larger ones elevated above the skin level, with a marginal induration of the subcutaneous tissues. The mucous membranes of the mouth and throat were normal; one small hemorrhage found on left conjunctiva and several retinal hemorrhages were revealed by an ophthalmoscopic examination. The larger ecchymoses had a purple center surrounded by a rose red areola, the intervening skin being much paler than normal.

The character, color and distribution of the eruption bore so striking a resemblance to the eruption in Case 1 as to suggest, in spite of the absence of the usual signs of meningeal involvement, the diagnosis of epidemic meningitis.

This diagnosis was corroborated by examination of the cerebrospinal fluid. Fifteen cubic centimeters of purulent fluid were obtained under increased pressure; the cell count was 22,500 per c.mm., 88 per cent. of the cells being of the polymorphonuclear variety. A direct smear of the sediment showed moderate numbers of gram-negative diplococci.

*Course.*—The progress of the case from this point may be briefly summarized: The child received 15 c.c. antimenigitis serum intraspinally on four successive days; the cells in the cerebrospinal fluid showed a gradual diminution in number, so that on June 15 the count was only 660 per c.mm. with 10 per cent. polymorphonuclears, and on June 19, 107 per c.mm. with 2 per cent. polymorphonuclears. Positive cultures of meningococci were obtained from the fluid taken at the first and fourth punctures. Blood culture obtained June 12



Fig. 5.—Taken on the eighth day of the disease, Case 2, showing a few of the larger lesions on left leg.

also showed a sparse growth of the same organism. The leukocyte count on June 12 was 18,500 per c.mm. with 80 per cent. polymorphonuclears; with each succeeding day there was a drop in the polymorphonuclear percentage, but the total count continued to range between 16,000 and 23,000 per c.mm.

The general improvement of the patient was immediate and striking, rigidity of the neck disappeared and she was able to sit up in bed unassisted six days after admission. The petechiae on June 21 had almost disappeared, nothing being visible but a faint brown pigmentation. Absorption of the subcutaneous hemorrhage around the larger areas was complete by June 21, and the lesion was at this time represented by a depressed scar capped by a reddish brown crust. Figures 4 and 5 are from photographs taken after the smaller lesions had almost disappeared and show a few of the larger individual lesions.

The child's recovery was complete and uncomplicated, she was discharged on June 30 and has continued to improve up to the time of writing.

## DISCUSSION

Unusual features of the two cases with additional facts of interest:

1. The character and distribution of the eruption, which was unlike the usual purpura hemorrhagica and which though differing greatly in degree was almost identical in both patients.

2. Paucity of other meningeal signs, such as opisthotonos and other manifestations of increased muscle spasm.

3. Demonstration of the specific organism in the blood of both patients, though attempts to grow the same organism from the skin lesions were unsuccessful.

4. Refutation of the old theory that the extent and color of the eruption was of prognostic aid. In both the above cases the meningeal manifestations were no more marked than usual, and were quite amenable to treatment.

5. Both cases were sporadic as far as could be learned by investigation of the locality and by a study of the Board of Health daily bulletin.

I am indebted to Dr. Holt, on whose service the cases were observed, for permission to publish this report.

## THE TONSILLAR MANIFESTATIONS IN THE EARLY DIAGNOSIS OF MEASLES \*

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What one does not look for one does not see. This is well illustrated in the case of the oral manifestations of measles. The disease is extremely common; numerous careful observers have examined innumerable patients and still the significance of certain manifestations for a long time escaped detection. I can find only three authors who have mentioned the tonsillar spots as an early manifestation of measles. Comby<sup>1</sup> reported four cases of measles in one family and described white spots (*angine pultacée*) as being present on the tonsils of two of these cases two days before the eruption appeared. Grumann<sup>2</sup> describes white spots or streaks about 3 mm. long which are present on the tonsils one or two days before the eruption. Miller<sup>3</sup> reports the case of a child which, when first examined, besides a rise of temperature, had dyspnea and a reddened throat. The tonsils were swollen and on each tonsil there were a number of small bluish semitransparent elevated bodies averaging considerably less than the size of the head of an ordinary pin. The eruption appeared the following day. No Koplik's spots were observed.

It is interesting to note that occasionally when these spots on the tonsils were seen, they were regarded as merely coincidental and their relation to the onset of measles not recognized. To cite one example, in von Pirquet's splendid monograph on measles two of Friedjung's cases are quoted to illustrate an unusually long period of incubation:

The first patient was taken sick on May 17, with a temperature of 39 C., apparently due to an angina lacunaris. May 18, 37.8 C., no change in the child's condition. May 19, 38.6 C., Koplik's spots and catarrhal symptoms. May 20, 39.5 C., beginning eruption. On June 2, the twin brother of the patient still showed no symptoms. On June 3, the temperature was 38.5 C. and there was an "angina lacunaris"; there were also a few indistinct Koplik's spots near the outlet of Stenson's duct. On June 4, 37.8 C. and an enanthema on the hard and soft palate. June 5, 38 C., no change. June 6, 39.6 C., beginning eruption.

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\* Submitted for publication July 15, 1915.

1. Comby: Arch. de méd. des enf., 1900, p. 420.

2. Grumann: München. med. Wchnschr., 1914.

3. Miller: Bull. Johns Hopkins Hosp., 1914, p. 78.

In both of these patients the tonsillar spots were present three days before the eruption, and in the first patient two days before the Koplik's spots.

In a paper recently published,<sup>4</sup> I mentioned that in ten cases of measles which I had seen in the early stage, four had presented the tonsillar spots, and that in two of these their appearance had preceded the Koplik's spots. During a recent epidemic I have had an opportunity to study this manifestation more carefully. Including the ten cases mentioned, I have now notes on 88 cases seen in the early stage; that is, at the beginning of the invasion. In eighty cases (90 per cent.) Koplik's spots were observed, in thirty-five cases (40 per cent.) the tonsillar manifestations were present. I should like to emphasize the fact that the patients must be seen in *the early stage, and the spots*

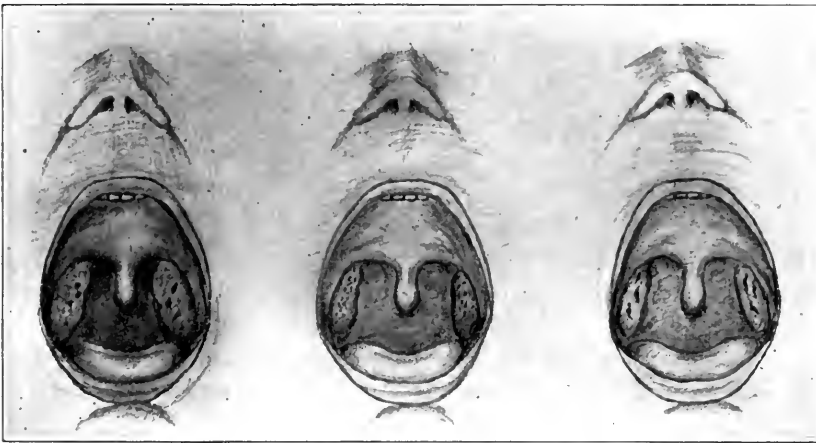


Figure 1

Figure 2

Figure 3

Tonsillar spots seen in the early stages of measles. Fig. 1.—A few round spots about the size of the head of a pin. Fig. 2.—A large number of very small spots or streaks. Fig. 3.—A few irregular streaks.

*must be looked for.* A good light is essential, the tongue must be depressed, and the tonsils must be examined. The tonsillar spots vary in number, size, shape, and color. There may be only two or three, or there may be twenty or thirty; they vary in size from the point to the head of a pin; they occur as round spots, as very small regular or larger irregular streaks (Figs. 1, 2, 3). The color seems to depend on the thickness, and varies from a bluish gray to white. They are seen only in the very early stage of the disease, and are visible one or two, occasionally three days. They are more frequently seen on enlarged

4. Herrman: Arch. Pediat., 1914, p. 885.

and succulent tonsils. The tonsils, as well as a small mass of lymphoid tissue on the soft palate just above and to either side of the uvula, frequently become hypertrophied at this stage of the disease. In the 35 patients in whom the tonsillar spots were observed, in 9 patients they were present one day before the eruption appeared; in 11 patients two days, in 7 patients three days, in 5 four days, in 2 six days, in 1 nine days before the eruption appeared.

In 30 of the 35 patients Koplik's spots were observed, in 14 patients one day before the eruption appeared, in 15 two days, in 1 three days before the eruption appeared.

In 13 patients the tonsillar spots were seen one day before Koplik's spots; in 3 two days, in 2 three days, in 1 four days, in 1 seven days before Koplik's spots.

In 5 patients the Koplik's spots were seen 1 day before the tonsillar; in 5 patients the Koplik's spots were seen on the same day as the tonsillar spots, and in 5 patients the Koplik's spots were not seen, so that the interval could not be determined.

In 12 patients the spots were visible for one day; in 17 two days, in 6 for three days.

At the time when the spots were first seen, the temperature was less than 100 in 6 patients, between 100 and 100.5 in 6, between 100.5 and 101 in 3, between 101 and 101.5 in 8, between 101.5 and 102 in 2, between 102 and 102.5 in 7, between 102.5 and 103 in 1, and between 103 and 103.5 in 2 patients.

It will be noted that in two-thirds of the patients the temperature was not over 101.5 at the time when the spots were first observed. This fact serves as a valuable point in differentiating the spots from those of follicular tonsillitis. In the latter the temperature is usually higher, the prostration is more marked, and there is usually an absence of catarrhal symptoms. In this disease also as the spots disappear the temperature falls; in measles, on the other hand, after the tonsillar spots disappear the temperature rises.

Not infrequently measles begins with an attack of croup and diphtheria may be suspected. If the tonsils show any spots, the suspicion may be increased; but in cases of measles the examination of the culture will be negative, and the rise in temperature and the increase in the catarrhal symptoms will clear up the diagnosis. In such cases, a knowledge of the appearance of the tonsillar spots of measles will be a valuable aid in differential diagnosis.

Taken altogether the tonsillar spots are much less valuable in the early diagnosis of measles than the Koplik's spots, first because they are present in only about 40 per cent. of the cases, and secondly,



because their appearance is not always so characteristic that they can be easily differentiated from those of follicular tonsillitis; but in families, classes, hospital wards, asylums in which other cases have occurred, or in which the disease is epidemic, it may be a very valuable aid in isolating the patients *early*. These spots are frequently present when the child has no other objective symptom except a slight rise of temperature.

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## THE TOTAL NONPROTEIN NITROGEN AND THE UREA OF THE BLOOD, AND THE PHENOLSULPHONE-PHTHALEIN EXCRETION IN CHILDREN \*

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The total nonprotein nitrogen of the blood has not been studied in children, so far as we are aware, and the urea of the blood has been determined only by the somewhat crude hypobromite method, to which, as Rowntree and Fitz<sup>1</sup> have shown, an error of from 10 to 60 per cent. attaches. We have therefore thought it worth while to investigate the blood in this respect, in various diseases of childhood and in healthy children. We have also investigated the phenolsulphonephthalein excretion, using the method of Rowntree and Geraghty. Owing to the small material available, the series is far from complete.

The term "nonprotein nitrogen" is synonymous with incoagulable nitrogen, rest or waste nitrogen and retention nitrogen, and designates the nitrogen of those substances remaining after the removal of the proteins. It includes the urea, creatinin, amino-acids, uric acid, and ammonia of the blood.

*Technic.*—For the nonprotein nitrogen and the urea nitrogen the methods of Folin and Denis<sup>2</sup> have been followed. Only a small amount of blood, from 2 to 5 c.c., is required. The blood was drawn from a vein of the arm or from the external jugular vein by means of a syringe. Whole blood was used, clotting being prevented by means of potassium oxalate. The figures are calculated in terms of milligrams of nitrogen per hundred cubic centimeters of blood. The values obtained for urea nitrogen include the ammonia nitrogen, which, however, is so small in amount in normal blood, and presumably in most cases of disease, as to be negligible.

In performing the phenolsulphonephthalein test, or as it will be called henceforth, for short, the phthalein test, the directions of Rowntree and Geraghty<sup>3</sup> were followed. The urine was obtained by catheter in every instance, the catheter being held in place by strips of adhesive plaster. This is necessary in the case of young children

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\* From the Department of Medicine, Yale University Medical School.

\* Read at the meeting of the American Pediatric Society, Lakewood, N. J., May 24, 1915.

1. Rowntree, L. G., and Fitz, R.: Arch. Int. Med., 1913, xi, 258.

2. Folin, O., and Denis, W.: Jour. Biol. Chem., 1912, xi, 527.

3. Rowntree and Geraghty: Jour. Pharm. and Exper. Therap., 1909, i, 579.

who will not urinate on command, and for the sake of uniformity of results, was done also in the case of the older children. The urine was collected separately for each of the first two hours after the injection, and the amount of the dyestuff was estimated in each of the two specimens.

The nitrogen and the urea determinations were made by Tileston, the phthalein estimations by Comfort.

*Total Nonprotein Nitrogen and Urea Nitrogen in Healthy Children.*—At first we took the blood in the morning, just before the noon meal, an arrangement which has proved satisfactory in the case of healthy adults, who show at this time from 22 to 26 mg. nonprotein nitrogen, about half of which is in the form of urea nitrogen.

We found in children, however, as will be seen by glancing at Table 1, a considerable variation at this time of day, in one case up to 34 mg. of nitrogen. We were led, therefore, in the case of children over 2 years of age, to take the blood before breakfast after a fast of twelve hours or more. In the two cases examined at this time there were 24.4 and 26 mg. of nitrogen and 9.5 and 10.9 mg. of urea nitrogen, respectively. The urea is seen to form somewhat less than one-half of the total nonprotein nitrogen, while if the influence of diet is not eliminated, the urea may constitute considerably more than one-half the total.

The influence of diet must therefore always be borne in mind in this kind of work, though in the case of children who are acutely sick, and taking in consequence less than the accustomed amount of food, we have found that the blood may be taken at any time of day without the liability of error.

*The Phenolsulphonephthalein Excretion in Healthy Children.*—The phthalein excretion in normal children has been found to vary from 35 per cent. to 64 per cent. for the first hour, and from 17 per cent. to 44 per cent. for the second hour. These wide variations are eliminated, however, if the total excretion for the two hours be considered, the figures then falling within very narrow limits, from 78 to 81 per cent. It is therefore evident that no conclusions can be safely drawn from this test unless the period of observation is extended to two hours. For practical purposes it will be sufficient to collect the urine for two hours in one vessel and make one determination of the phthalein.

The phthalein excretion in healthy children is considerably higher than in the adult, where values anywhere from 50 to 80 per cent. are considered normal.

A word of explanation is necessary in connection with the urine examinations in Table 1. The presence of red cells and a slightest

possible trace of albumin is accounted for in some instances by the fact that a catheter has been passed previously. In other cases it is the normal albuminuria which can usually be demonstrated in health by the nitric acid test, if done by an expert.

*Acute Nephritis.*—Owing to the small size of the clinical material, we have but three cases of nephritis to report, all acute. The first was a case of scarlatinal nephritis in a girl 8 years old. The history was vague, fever having been remarked a week before entrance to the hospital, and swelling of the feet five days later, but no rash. The diagnosis was cleared up later by the appearance of typical desquamation of the feet. Mild uremic symptoms were present, such as prostration, drowsiness and vomiting. The eyelids were puffy, but there was no edema elsewhere. The examination of the urine indicated an acute nephritis of considerable severity, showing 0.3 per cent. albumin, with many brown granular and hyaline casts, red blood corpuscles and leukocytes. Both the nitrogen and the urea were markedly increased, the former measuring 64 and the latter 43 mg. The phthalein excretion was 39 per cent. in two hours. A month later the nitrogen had fallen to normal and the albumin to a very slight trace, and she was discharged well soon afterward.

The second case was one of unknown origin and moderate severity, in a boy 9 years old. The only symptoms were puffiness of the face and albuminuria. The urine showed a large trace of albumin, with many blood and granular casts, red blood cells and leukocytes. There was a slight elevation of the blood nitrogen (34.5 mg.) and of the urea (21 mg.). The phthalein output was 56 per cent. in two hours. The albumin dropped in a few days to a slight trace, the casts and red cells being still numerous. He was discharged at the end of two weeks with only the slightest possible trace of albumin and a few casts.

The third case occurred as a complication of lobar pneumonia, in a boy 30 months old. He entered the hospital on the eighth day of the disease, the crisis occurring next day. There was a large trace of albumin in the urine, with hyaline, granular and epithelial casts, and red blood cells. The blood nitrogen and urea were normal and the phthalein excretion over 54 per cent. (some urine lost). Five days later the albuminuria had nearly disappeared and he was discharged well soon after. This case might be regarded as one of febrile albuminuria by some, on account of its prompt subsidence, but the large amount of albumin, together with the frequency of nephritic changes (especially glomerulonephritis) at postmortem examinations of such cases, would appear to justify the diagnosis.

The cases, so far as they go, indicate that nephritis when accompanied by uremic symptoms tends to show a marked increase in the

TABLE I.—NORMAL CASES \*

Name	Case No.	Sex	Age	Diagnosis	Phenolphthalein		Urine		Diet	Blood		Remarks
					Per Cent. in 1st Hr.	Per Cent. in 2d Hr.	Sp. Gr.	Alb.		Total N, Mg.	Urea N, Mg.	
Leissenhaltz..	1	M	7	Fractured leg. . .	64	17	1.031	S. P. T.	Many W. B. C. and R. B. C.	20.2	10.5	Blood taken at noon.
Juliano.....	2	M	9	Fractured arm....	58	20	1.020	S. P. T.	Negative.....	24.4	9.5	Blood taken fastling.
Ferraro.....	3	M	4½	Fractured femur..	35	44	1.025	S. P. T.	Negative.....	26.0	10.9	Blood taken fastling.
Mellio.....	4	M	3	Burn of eye.....	52	27	1.030	S. P. T.	W. B. C. ....	31.9	17.8	Blood taken at noon.
Dest. ....	5	M	3	Phimosis.....	..	..	1.018	0	Negative.....	34.0	19.6	Blood taken at noon.

\* The following abbreviations are employed in this and following tables: S.P.T. = slightest possible trace; V.S.T. = very slight trace; S.T. = slight trace; H.T. = heavy trace; W.B.C. = white blood corpuscles; R.B.C. = red blood corpuscles; the figures for albumin were obtained by the Esbach method, and represent percentages.

TABLE 2.—NEPHRITIS

Name	Case No.	Sex	Age	Diagnosis	Day of Dis- ease	Phenolphthalein			Urine		Diet	Blood		Remarks
						Per Cent. in 1st Hr.	Per Cent. in 2d Hr.	Total in 2 Hrs.	Sp. Gr.	Alb.		Total N. Mg.	Urea N. Mg.	
Faust.....	6	M	2½	Acute nephritis, complicating acute lobar pneumonia	9	40	14+	54+	1.026	H. T.	Liquid..	26.2	13.6*	T. = 99.7 F.
Lucibello....	7	M	9	Acute nephritis...	11	19	37	56	1.027	S. P. T.	.....	....	....	Fivedays later.
Dunn.....	8	F	8	Acute nephritis, complicating scarlatina	4-9	..	..	39	1.015	H. T.	Low pro- tein	34.5	21.0	T. = 99 F. Eti- ology un- known
									1.010	0.3 %	Liquid..	63.6	42.9	T. = 98.6 F.
									1.013	V. S. T.	Liquid..	31.0	....	T. = 98.6 F. thirty days later.

\* One determination.

TABLE 3.—PNEUMONIA

Name	Case No.	Sex	Age	Diagnosis	Day of Dis- ease	Phenolphthalein			Urine			Diet	Blood		Remarks
						Per Cent. in 1st Hr.	Per Cent. in 2d Hr.	Total in 2 Hrs.	Sp. Gr.	Alb.	Microscopical		Total N, Mg.	Urea N, Mg.	
Carbone....	9	F	4	Pneumonia, acute lobar	6	5	40	45	1.024	V. S. T.	Very many W.B.C.....	Soft.....	20.2	13.3	Temp. 105.4 F.
Katz.....	10	M	15mo.	Pneumonia, acute lobar	9	5	12	17		S. P. T.	Granular casts; W.B.C.	Formula	22.2	12.9*	Temp. 104 F.
Szeresnowicz	11	M	9	Pneumonia, acute lobar	5	..	..	68	1.024	S. P. T.	W.B.C. ....	Soft.....	23.1	11.8	Temp. 101.2 F. Crisis ended next day. Moderately severe case
													24.0	12.6*	Temp. 98.6 F.
Grauel.....	12	F	8	Pneumonia, acute lobar	..	..	..	63	1.020	V. S. T.	Occasional hyaline cast and R.B.C.; W.B.C.	Very soft	24.4	13.8	Temp. 100 F.
Rumano....	13	M	9	Pneumonia, acute lobar	11	55	30	85	1.025	S. P. T.	Occasional R.B.C.; few W.B.C.	Soft.....	24.7	10.4	Temp. 102 F.
Knudsen....	14	F	8 mo.	Pneumonia, acute lobar	8	..	..	53		S. P. T.	Rare hyaline and granular casts; few R. and W.B.C.	Formula	25.6	11.7	Temp. 102 F. Empyema later.
Malvedo....	15	M	6 mo.	Pneumonia, acute lobar	8	..	..	..		S. P. T.	Negative.....	Formula	28.3	14.6	Temp. 105 F. Died next day.
Levy.....	16	M	5	Pneumonia, acute lobar	3	..	..	70	1.020	S. P. T.	Rare hyaline cast; numerous W.B.C.	Soft.....	29.7	21.2	2/22/15. Temp. 104 F.
													27.8	15.2*	2/24/15. Temp. 99 F.
Zoufman....	17	M	8	Pneumonia, acute lobar	7	..	..	57	1.025	S. P. T.	Occasional fine granular and hyaline cast and R.B.C.; W.B.C.	Soft.....	32.6	19.8	Temp. 103 F.

TABLE 4.—SCARLATINA AND TYPHOID FEVER

Phenolphthalein														
Name	Case No.	Sex	Age	Diagnosis	Day of Dis- case in 1st Hr.	Per Cent. Total		Urine		Diet	Blood		Remarks	
						in 1st Hr.	in 2d Hr.	Sp. Gr.	Alb.		Total N, Mg.	Urea N, Mg.		
Russell.....	18	M	7	Scarlatina.....	5da.	..	..	1.028	0	Negative.....	Soft.....	21.7	10.1	Temp. 103.5 F. Moderately severe case.
Vaughn.....	19	F	10	Scarlatina.....	4da.	..	..	1.018	S. P. T.	Negative.....	Soft.....	23.2	10.9	Temp. 100.8 F. Moderately severe case.
Miller.....	20	M	11	Scarlatina.....	3da.	42	40	1.029	S. P. T.	W.B.C. ....	Liquid..	26.6	15.3	Temp. 99 F. Blood taken fasting. Mild case.
Dowd.....	21	F	7	Scarlatina.....	5da.	..	..	1.032	V. S. T.	Few hyaline and gran- ular casts; W.B.C.	Liquid..	26.7	15.1	Temp. 100.8 F. Mild case.
Koskoff, Y.	22	M	9	Scarlatina.....	3da.	26	46	1.027	S. P. T.	W.B.C. ....	Liquid..	26.9	16.3	Temp. 102.8 F. Blood taken fasting. Mod- erately severe case.
Seandore...	23	F	17mo.	Scarlatina.....	5da.	44	5+		S. P. T.	W.B.C. ....	Liquid..	27.8	13.6*	Temp. 101 F. Mild case.
Cohen.....	24	F	3	Scarlatina.....	3da.	40	34	1.024	S. P. T.	Fine granular casts; rare R.B.C.; W.B.C.	Soft.....	28.1	14.2*	Temp. 102.5 F. Moderately severe case.
Koskoff, L.	25	F	5	Scarlatina.....	1da.	35	39	1.018	0	Negative.....	Liquid..	28.5	15.4	Temp. 101 F. Blood taken fasting. Mild case.
Weinstein..	26	F	7	Scarlatina.....	2da.	55	31	1.032	0	Negative.....	Soft.....	29.1	13.8	Temp. 101 F. Moderately severe case.
Bartholomew	27	M	10	Scarlatina.....	5da.	..	..	1.030	S. P. T.	Negative.....	Soft.....	31.9	....	Temp. 99 F. Mild case.
Gentile.....	28	M	3	Typhoid fever....	10da.	31	32	g.n.s.	S. P. T.	W.B.C. ....	Typhoid	21.9	10.3	Temp. 101.04 F. Blood taken fasting.
Daniels.....	29	F	8	Typhoid fever....	10da.	48	24	1.026	S. P. T.	Few W.B.C. ....	Typhoid	22.7	11.1	Temp. 104 F. Blood taken fasting.
Wilens.....	30	M	8	Typhoid fever....	7 da.?	..	..	1.010	V. S. T.	W.B.C. ....	Typhoid	22.7	11.9	Temp. 104 F. Blood taken fasting.
Cruscola....	31	F	5	Typhoid fever....	5 wk.	56	8	1.012	S. P. T.	Occasional granular cast; few R. and W.B.C.	Typhoid	25.0*	....	Temp. 102 F.
Daddio.....	32	M	5	Typhoid fever....	8da.	21+	36+	1.028	S. T.	Occasional fine granu- lar cast; R.B.C.	Typhoid	29.0	14.2	Temp. 99-102 F.
Gladwin....	33	F	10	Typhoid fever....	12 da.	..	..	1.020	V. S. T.	Hyaline casts; few R.B.C.; W.B.C.	Typhoid	29.2	15.8	Temp. 103 F.

\* One determination.



TABLE 5.—MISCELLANEOUS DISEASES

Name	Case No.	Sex	Age	Diagnosis	Phenolphthalein			Urine			Diet	Blood		Remarks
					Day of Dis. case in 1st Hr.	Per Cent. in 2d Hr.	Total in 2 Hrs.	Sp. Gr.	Alb.	Microscopical		Total N, Mg.	Urea N, Mg.	
Brazen.....	34	M	3½	Diphtheria.....	1 da.	..	..	1.020	0	Negative.....	Liquid..	25.3	13.9	Temp. 102.8 F Mild case.
Peck.....	35	M	8	Diphtheria.....	3 da.	61	15	1.020	S. P. T.	Few hyaline casts and W.B.C.; rare R.B.C.	Liquid..	28.4	14.1	Temp. 99 F. Severe case. Complicated later by myo-carditis.
Sinclair.....	36	F	8	Pertussis.....	3 wk.	24	6	1.026	0	Occasional W.B.C.....	Liquid..	23.6	11.9	Temp. 102.4 F. Complicated by broncho-pneumonia. Temp. 99 F. Blood taken fasting.
Campagne..	37	F	6	Tuberculous neck glands	3 mo.	51	19	1.026	S. P. T.	Few W.B.C.....	Mixed...	21.4	....	Temp. 98.6 F. Blood taken fasting.
Frabianna..	38	F	2	Tuberculous perit. tonsitis	6 wk.	..	..	..	S. P. T.	Few granular casts and R.B.C.; many W.B.C.	Soft.....	27.2	12.0	Temp. 102 F.
Daniels.....	39	F	8	Tuberculous hip..	1 yr.	..	..	1.022	S. P. T.	Rare R.B.C.; W.B.C..	Soft.....	27.2	....	Temp. 98.6 F.
Ryan.....	40	M	5	Tuberculous hip ..	38	45	83	1.022	0	Negative.....	Soft.....	32.0	17.3	Blood taken fasting.
Masorka....	41	F	13 mo.	Tuberculous men- ingitis	2 wk.	..	..	....	....	....	Formula	21.2	10.3	
Makarias...	42	F	1 mo.	Tuberculous men- ingitis	1 wk.	56	23	79	S. P. T.	Many R. and W.B.C. .	.....	27.5	14.2	Temp. 102 F.
Alberino....	43	F	10	Tuberculous men- ingitis	5 da.	..	..	1.022	V. S. T.	Rare hyaline cast; W.B.C.	Liquid..	31.6	14.1	Temp. 102.8 F.
Vilow.....	44	M	4	Cerebrospinal meningitis	4 da.	63	15	1.015	V. S. T.	Rare granular casts; R. and W.B.C.	Soft.....	25.9	11.4	Temp. 101.8 F.
Hathaway..	45	F	7	Keratitis; congeni- tal lues	8 wk.	..	..	1.022	S. T.	Few W.B.C.....	Mixed...	23.4	13.6	Temp. 99 F.
Lavalle.....	46	M	8	Endocarditis and pericarditis, rheu- matic	..	..	..	1.022	S. P. T.	Few hyaline casts; W.B.C.	Soft.....	22.7	11.0	Temp. 102 F.
Weiss.....	47	F	6½	Chorea.....	2 wk.	..	..	1.025	0	Negative.....	Low pro- tein	23.6	12.1	Temp. 99 F. Blood taken fasting.
Mazzamotti	48	M	6	Rickets.....	..	63	15	1.023	S. P. T.	Few W.B.C.....	Soft.....	23.4	10.6	Blood taken fasting.
Ruscetti.....	49	M	2½	Rickets, gastro- enteritis	2 mo.	43	29	72	1.016	S. P. T.	W.B.C.....	26.9	12.7	Temp. 102 F. Blood taken fasting.
Dyllsi.....	50	F	4	Rickets.....	..	..	..	1.018	0	Negative.....	Mixed...	22.7	18.1*	Temp. 102.2 F.
Ferrucci....	51	F	8	Ichthyosis .....	8 yr.	..	..	1.015	S. P. T.	Many R. and W.B.C..	Mixed...	21.5	11.7	Temp. 98 F.

\* One determination.

total nitrogen and urea. In the cases without uremic manifestations, on the other hand, the increase is slight or absent. The phthalein appears to vary roughly with the degree of impairment of renal function.

*Acute Lobar Pneumonia.*—In this disease nine out of ten patients showed no increase whatever in the total nitrogen; in the tenth case there was a trifling increase up to 33 mg. The urea was normal in eight cases, and moderately increased in two. This is contrary to our experience<sup>4</sup> in the pneumonia of adults, where 70 per cent. of those over 21 years of age showed more than 35 mg. of nitrogen. A fatal case in an infant of six months showed normal figures for both nitrogen and urea the day before death, as did also the case complicated with nephritis, already alluded to in the section on nephritis.

The phthalein excretion in pneumonia varied from 17 to 85 per cent. for two hours, the average being 57 per cent. The case with 17 per cent. excretion showed only a slightest possible trace of albumin and 22 mg. of nitrogen, not differing either clinically or with respect to the blood and urinary findings from the case with 85 per cent. excretion. The child with nephritis showed over 54 per cent. phthalein. These facts illustrate the danger of drawing conclusions from a single application of the phthalein test in acute conditions.

*Scarlatina.*—We were particularly interested in this disease, on account of the frequency with which nephritis occurs as a complication. Contrary to our expectations, we found practically normal values in all of the ten cases not complicated by nephritis, the highest figure for nitrogen being 32 mg. and the highest for urea 16 mg. The case of scarlatinal nephritis has been described already, in the section on nephritis.

The phthalein excretion in the cases without nephritis averaged 75 per cent., a much higher figure than that obtained in pneumonia (57 per cent.).

*Typhoid Fever.*—Six cases of typhoid fever all showed normal values for both nitrogen and urea. The phthalein excretion averaged 68 per cent.

We have also examined instances of diphtheria, pertussis with bronchopneumonia, tuberculosis of various tissues, cerebrospinal meningitis, hereditary syphilis, rheumatic pericarditis, chorea, rickets and ichthyosis; all with negative results.

#### CONCLUSIONS

1. The determination of the total nonprotein nitrogen and urea of the blood is of great assistance in the diagnosis of uremia, and as a guide to the treatment of nephritis, a marked increase in these sub-

4. Tileston and Comfort: Arch. Int. Med., 1914, xiv, 620.

stances indicating actual or impending uremia, and calling for a diet low in protein. In the diagnosis of nephritis it is inferior to other methods, because many cases of nephritis show no retention of nitrogen.

2. The phthalein test is very valuable in the diagnosis of nephritis, showing probably better than any one other method the degree of impairment of renal function. In the diagnosis of uremia and as a guide to diet it is inferior to blood analysis, for a low phthalein output may occur without retention of nitrogen.

3. These investigations of the blood and of the phthalein excretion would appear to indicate a better secreting capacity of the child's kidney as compared with that of the adult.

# THE ATROPIN TREATMENT FOR THE EXUDATIVE DIATHESIS IN INFANCY \*

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Some years ago Czerny gave the name of "Exudative Diathesis" to a group of symptoms characterized by an exudation into the skin and mucous membranes. The skin of infants suffering from exudative diathesis shows some form of eczema, varying in grade from a very mild seborrhea to extensive infiltration, with excoriation. The so-called geographic tongue is seen in some cases. Catarrhal affections of the respiratory tract—coryza, pharyngitis, recurrent bronchitis, and asthma—make their appearance. A catarrh of the gastrointestinal tract is often present. General glandular enlargement with an enlarged spleen may be combined with one or more of the other manifestations. An eosinophilia is found in the blood examination of some of the cases. The exudative diathesis is generally encountered either in very obese or in very thin infants; some of the cases, however, are normal in weight and development.

The eczema, bronchitis and asthma occurring in infants with other symptoms of exudative diathesis are occasionally very resistant to the ordinary methods of treatment. The very fat, overfed babies are at times greatly improved by reduction in diet with consequent loss in weight. The symptoms occurring in poorly nourished infants occasionally clear up rapidly with proper regulation of the diet and gain in weight. In both classes of cases external treatment of the eczema in the form of ointments is used in combination with the dietetic therapy. With the most careful combined treatment, however, a certain proportion of the cases fail to improve. The eczema persists for many weeks, months, or even years, and there are recurrent attacks of asthma, bronchitis, and pneumonia. It is for these patients that the atropin treatment is advocated.

## ATROPIN TREATMENT

Before detailing my results a brief review of the development of the atropin therapy should be given. Although the cause of the exudative diathesis is unknown,<sup>1</sup> Eppinger and Hess believe that it is

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\* From the Hebrew Infant Asylum, New York City.

1. According to Czerny, "exudative" infants are born with a constitution different from normal infants. Metabolism studies on these infants have varied a good deal, and have thrown very little light on the cause.

an infantile form of vagotonia, and various manifestations are thus due to increased tone in the vagus system. With this theory in mind, Krasnogorski treated a number of infants, ill for many months with the manifestations of exudative diathesis, with atropin, a drug causing, as is well known, decrease of vagus irritability. Six infants, all under 9 months of age, were treated. Four of them had suffered from severe grades of eczema and two from bronchitis and asthma. Cures followed administration of atropin in all these infants. No toxic effects such as flushing and dryness of the skin, dilatation of the pupils, tachycardia, etc., were observed, and Krasnogorski therefore concluded that infants suffering from exudative diathesis were very tolerant to the drug.

During the past year I have administered the atropin treatment to ten infants suffering from symptoms of the exudative diathesis—severe eczema, bronchitis or asthma. Mild cases were not treated, for I believe that the best test of the efficacy of the atropin therapy would be the advanced and pronounced cases. The patients were all institutional babies ranging in age from 4 months to 2 years, and were under constant medical supervision. Careful observations were made on the condition of the pupils, skin, pulse rate, etc. Temperatures were recorded several times daily. The infants under 1 year were weighed daily, and the older infants once or twice weekly. As the accompanying case reports will show, the results of the atropin treatment on the lesions of the exudative diathesis were excellent; and this despite the fact that no changes in diet were made, and no other drugs administered. One infant (Case 9) died during the period of observation. In this patient atropin had a beneficial effect on the eczema, but in no wise influenced the pulmonary condition, death following a terminal bronchopneumonia.

*Method of Administration.*—Atropin was used in a solution of 1 grain of atropin sulphate to 480 drops of water.<sup>2</sup> Three drops of this solution were given on the first day of treatment, and if no untoward effects were observed, the dose was increased 1 drop daily until patients received about 30 drops daily (equivalent to 1/16 grain of atropin sulphate). This last dose was given daily for one or more weeks until the manifest signs of the exudative diathesis had disappeared. Smaller doses were then administered for a few more days or weeks. In only one case (Case 2) did untoward manifestations appear; they were very mild, and did not recur after the initial dose of the atropin solution had been reduced. In no case was there any harmful result from the atropin treatment. It was clearly evident from the beginning that infants suffering from exudative diathesis

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2. In one case a 1:960 solution was used.

were able to take large doses of atropin sulphate without showing toxic effects.

Whether the theory of Eppinger and Hess prove true or false, the fact remains that striking results were obtained in my series of cases by atropin treatment administered on that theory. From a study of these cases it is fair to conclude that atropin sulphate in increasing doses given over long periods of time is of great value in the treatment of those severe and obstinate manifestations (eczema, bronchitis, asthma) of the exudative diathesis which do not respond to the ordinary dietary and local treatment. It will be my further object to determine if repeated courses of atropin are required or if a single course will effect a permanent result.

#### CASE REPORTS

CASE 1.—Aged 11 months. One of triplets. Weight  $12\frac{1}{4}$  pounds. On modified milk mixture. Evidences of rachitis. There was present a very marked generalized eczema, and an intertriginous eczema in the inguinal region, and over the buttocks. A history of recurrent attacks of bronchitis was given.

*Treatment.*—One drop of a solution of atropin sulphate 1:480 three times daily, increasing one drop each day. After four weeks 30 drops of the solution ( $\frac{1}{16}$  of a grain) were given daily. This dose was continued for four days when slight flushing of the skin, some regurgitation of food, and tachycardia set in. The atropin was then reduced to 24 drops daily. The toxic symptoms did not reappear and the dose was kept up for ten days. Atropin was then discontinued. The eczema had entirely cleared up and there were no attacks of bronchitis. Two months later the general condition was excellent; weight  $15\frac{1}{4}$  pounds, and there were no signs of the exudative diathesis.

CASE 2.—Aged 11 months. Weight 14 pounds. On modified milk mixture. There were present a marked generalized eczema, and a diffuse bronchitis.

*Treatment.*—The infant first received 1 drop of a solution of atropin sulphate 1:480 three times daily. With this dose there was slight flushing of the skin, dilated pupils, and a rapid pulse. One drop of a 1:960 solution was then given. There was no reaction with this dose. It was increased one drop daily until the infant was receiving at the end of forty-one days, 44 drops daily (corresponding to about  $\frac{1}{20}$  grain of atropin). This dose was continued for ten days without any reaction. The bronchitis had completely cleared up and the eczema was markedly improved after one week. One-sixteenth grain of atropin was then given for one week without any reaction. Then  $\frac{1}{20}$  grain was given for sixteen more days. The drug was then stopped. Twice during this period there were slight attacks of bronchitis which lasted four and five days, respectively. The eczema was completely controlled after eight weeks' treatment. One month after treatment had been stopped there had been no recurrences of the eczema or bronchitis.

CASE 3.—Aged 2 years. Weight 25 pounds. Regular diet. Very well developed child. There was a severe papular-vesicular eczema on both cheeks. This eruption extended around the left ear. There was a patch of eczema in the left auditory canal. There were lesions characteristic of lichen urticatus on both arms. The skin lesion had been of four months' duration and was gradually getting worse.

*Treatment.*—One drop of atropin solution 1:480 was given three times daily. This was increased one drop daily. After eighteen days the dose was 20 drops daily, or  $\frac{1}{24}$  grain of atropin. There was never any untoward reaction. After

three days' treatment the eczema was markedly improved, and after two weeks' treatment it had almost cleared up. There still remained a slight grade of erythema which responded to the application of silver nitrate and Lassar's paste.

CASE 4.—Aged 12 months. Weight 17 pounds. Regular diet. A severe papular eczema was present on the face and lower extremities. There was also a seborrheal eczema of the scalp.

*Treatment.*—Atropin sulphate, 1 drop three times daily of a 1:480 solution, was given, increasing one drop daily. After two weeks the infant was receiving 18 drops daily ( $\frac{3}{80}$  grain). This dose was given for four days and then decreased 1 drop daily because the eczema showed such marked improvement. The eczema cleared up entirely after two weeks' treatment. The atropin was given for five weeks and then stopped. There had been no recurrence after two months. During the previous three and one-half months the infant gained  $5\frac{1}{2}$  pounds. Its general condition was excellent.

CASE 5.—Aged 7 months. Weight 16 pounds. On a simple milk mixture. Rachitic infant. Geographic tongue. Severe eczema of both lower extremities and over entire body. Face clear. Slight scaling of scalp.

*Treatment.*—The infant received 1 drop three times daily of a 1:480 solution of atropin sulphate, which was increased 1 drop daily until 10 drops were given daily. The atropin was stopped after fifteen days, when the eczema was completely cured. Three months after treatment had been stopped there had been no recurrence of the eczema. The infant's general condition was very good. It weighed  $20\frac{1}{2}$  pounds.

CASE 6.—Aged 4 months. Weight  $14\frac{1}{2}$  pounds. On buttermilk feedings. There was present a severe eczema of the scalp, face, and buttocks. There were many asthmatic râles present throughout both chests.

*Treatment.*—Infant received atropin sulphate solution in increasing doses until 16 drops were given daily. With this dose (grain  $\frac{1}{30}$  of atropin) there was slight flushing of the skin. The pupils were dilated at times. After seven days' treatment the lungs were entirely clear and the infant's general condition was much improved. The eczema was practically controlled. The atropin was discontinued after fourteen days' treatment, when all signs of eczema and asthma had disappeared. Four months after treatment had been stopped the infant weighed  $17\frac{1}{2}$  pounds. There had been no recurrence of the eczema or asthma. The general condition of the infant was excellent.

CASE 7.—Aged 7 months. Weight 15 pounds. On buttermilk and cereal feedings. There were present many asthmatic râles throughout both chests. There was some scaling of the scalp.

*Treatment.*—Atropin sulphate solution 1:480 was given beginning with 1 drop three times daily, and increasing 1 drop daily until 15 drops or about  $\frac{1}{30}$  of a grain was given daily. With this dose there was slight flushing of the skin. The dose was then reduced to  $\frac{1}{48}$  of a grain daily, and this dose was given for two weeks and then stopped. The asthma was completely cured after one month's treatment. One month after treatment had been stopped the infant had another attack of asthma. Atropin sulphate was given again, beginning with 5 drops three times daily. This dose was increased daily until the infant was receiving 30 drops, or  $\frac{1}{16}$  grain daily. The attack of asthma was cured in one week. Six weeks after treatment was stopped the infant's condition was excellent, and it had had no more attacks of asthma.

CASE 8.—Aged 15 months. Weight  $23\frac{1}{2}$  pounds. On regular diet. There was a history of recurrent attacks of asthma. There was some scaling of the scalp. Both chests were filled with asthmatic râles.

*Treatment.*—Atropin sulphate solution was given in increasing doses until the infant was receiving  $\frac{1}{16}$  of a grain daily. The asthma was completely cured in nine days. Two months after treatment had been stopped there had been

no recurrence of the asthma. The infant weighed  $25\frac{1}{2}$  pounds. Its general condition was excellent.

CASE 9.—Aged 11 months. Weight  $14\frac{1}{2}$  pounds. On regular diet. Very poorly developed infant with marked rachitis. Severe generalized seborrheal eczema. For two weeks severe diffuse bronchitis. Pirquet reaction negative. Coughed a good deal. Temperature between 98 and 103.8 F. Respirations between 28 and 80.

*Treatment.*—Infant received one drop of a 1:480 solution of atropin sulphate three times daily, increased one drop daily until about  $\frac{1}{30}$  of a grain of atropin sulphate was given each day. After five days' treatment the eczema was somewhat better. The bronchitis remained the same. After two weeks' treatment the eczema was completely controlled, but the diffuse bronchitis persisted. During this period the infant gained 10 ounces in weight. The temperature and respirations continued about the same. Finally a bronchopneumonia developed and the infant died. In this patient atropin controlled the eczema, but had little, if any, effect on the pulmonary condition.

CASE 10.—Aged  $10\frac{1}{2}$  months. Weight 12 pounds. On a regular diet. Rachitic infant. No teeth. The infant had marked beading of the ribs, craniotabes and a markedly distended abdomen. Muscles flabby. The liver and spleen palpable. Geographic tongue. Marked scaling of the scalp. Severe papular eczema of chest. Intertriginous eczema of folds of neck. Very severe asthma of both chests. Temperature between 98.6 and 101.6 F.

*Treatment.*—One drop of atropin sulphate solution (1:480) was given three times daily until the infant was receiving about  $\frac{1}{30}$  grain of atropin daily. With this dose there was at times dilatation of the pupils and slight flushing of the skin. One-thirtieth grain of atropin was given daily for a period of three weeks, and was then discontinued. The infant's condition gradually improved under atropin treatment. After sixteen days' treatment the eczema was controlled and the lungs were almost clear. After five weeks' treatment the eczema had entirely disappeared and the asthma was cured. During the atropin period the infant gained 2 pounds in weight.

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# PROGRESS IN PEDIATRICS

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## EXUDATIVE DIATHESIS—A REVIEW \*

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### HISTORICAL

The idea of the diatheses is very old (His<sup>1</sup> and Krehl<sup>2</sup>). It played a prominent rôle in the medicine of ancient Greece, especially the school of Galenus, and it persisted up to the beginning of the modern scientific study of the natural phenomena, when exact examination took the place of philosophic speculation and when Virchow's cellular pathology and the widespread use of the microscope dislodged the constitutional theory.

At the beginning of the present century the German school of medicine resurrected these old theories, which had always been adhered to by the French, and medical writers in Europe, especially in these two countries, have given ample expression to the ideas of disposition and constitution. In pediatrics as well as in dermatology these theories have helped us to understand many a clinical picture which would otherwise have remained veiled.

### THE DIATHESES

The term diathesis attempts to give expression to the internal relations of heterogeneous groups of diseases, due to individual conditions, which are usually congenital, often hereditary. In these physiologic stimuli cause an abnormal reaction and morbid phenomena under normal conditions of life.

At present we are able to recognize only certain groups of symptoms, to which we give the name of a diathesis; such as arthritism, lithemia, exudative diathesis, spasmophilia, status thymicolymphaticus, mongolism, infantilism, eosinophilia, some neuropathies, hemophilia; perhaps also epilepsy, chlorosis and the hypoplasias of the aortic system (His<sup>1</sup>).

The French school of medicine recognizes the *diathèse arthritique*. This they regard as a disease of the intellectual classes, of those with sedentary habits, and therefore a disease of degenerating races.

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1. His, W.: *Geschichtliches und Diathesen in der inneren Medizin*, Deutsch. med. Wchnschr., 1911, xxxviii, 857.

2. Krehl, A.: *Med. Klin.*, 1911, vii, 752.

Comby<sup>3</sup> considers arthritism as a morbid temperament which is dormant in childhood and does not appear until adult life; in childhood, however, the symptoms of the hereditary taint will be observed under the guise of imperfect nutrition, incomplete development, hypertrophies or hyperplasias, a defective arterial system, and an abnormal and easily vulnerable connective tissue.

Hutinel<sup>4</sup> states that it is, at present at least, very difficult to define arthritism. It is not a disease, but a morbid temperament, a peculiar form of metabolism.

De Monchy<sup>5</sup> thinks that arthritism and exudative diathesis should be clearly separated, even more so than has been done by Czerny.

Galup<sup>6</sup> brings arthritism in relation to anaphylactic phenomena.

In English and American medicine we find under the name of lithemia the symptoms which French writers collect under arthritism, Rachford.<sup>7</sup> Others, for instance Whitmore,<sup>8</sup> describe under lymphatism the status thymicolymphaticus, or they recognize this latter condition only, as for instance Holt.<sup>9</sup>

The majority of the writers in the English language, however, fail to mention the diatheses altogether. This neglect is now beginning to be recognized. Cameron<sup>10</sup> deplors this fact and shows the importance of the diatheses on infant feeding and infant mortality.

Dutch literature is also rather wanting on the subject of the diatheses. Some, like Sthemann,<sup>11</sup> refuse to recognize their revival, while others, like Gorter,<sup>12</sup> take a standpoint somewhat between the French and German schools.

3. Comby, J.: *Arthritisme*; Grancher et Comby, *Traité des Maladies de l'Enfance*, Paris, 1904, i, 770.

4. Hutinel, V. and Tixier, L.: *Arthritisme.—Etat lymphatique*. In V. Hutinel's *Les Maladies des Enfants*. Volume 2, pages 612 and 688, Paris, 1909, ii, 612.

5. de Monchy: *Diathesen bei Kindern*, reviewed in *Jahrb. f. Kinderh.*, 1911, lxxiv, 468.

6. Galup, J.: *Le lymphatisme. Diathèse d'anaphylaxie-immunité. Une conception générale des diathèses*, reviewed in *Ztschr. f. Kinderh.*, 1913, Referate, v, 668.

7. Rachford: *Lithaemia*, *Arch. Pediat.*, August, 1897: *Symptomatology of Lithemia*, *Arch. Pediat.*, September, 1897.

8. Whitmore, A.: *Lymphatismus in the East*, *Lancet*, London, 1911, clxxxi, 752.

9. Holt, E.: *Diseases of Infancy and Childhood*, Ed. 5, New York, 1910.

10. Cameron, H. C.: *On Diathesis in Infancy; a Plea for Its Closer Study*, *Brit. Med. Jour.*, 1914, p. 53.

11. Sthemann: *Konstitutionsanomalien bei Kindern.*, *Jahrb. f. Kinderh.*, 1911, lxxiv, 576.

12. Gorter, E.: *Ueber exsudative Diathese, Lymphatismus und skrophulöse Konstitution*, reviewed in *Jahrb. f. Kinderh.*, 1911, lxxiii, 271.

Since the memorable paper of Czerny,<sup>13</sup> published ten years ago, in which he first mentioned the name of *exudative diathesis*, many monographs have been published on the subject of the diatheses, and their importance in medicine has, by some at least, been fully appreciated.

Some German authors, like Pfaundler,<sup>14</sup> consider it a mistake to confound diathesis with dyscrasia, and the symptoms of a diathesis with the diathesis itself.

Von Behring<sup>15</sup> confines the term diathesis to only a small part of the disposition. He considers a diathesis as an individual, congenital, often inherited condition, in which physiologic stimuli cause an abnormal reaction.

Klotz<sup>16</sup> considers the status lymphaticus to be an extreme type of exudative diathesis.

Sittler<sup>17</sup> states that exudative diathesis is found so frequently in children nowadays that one might feel inclined to regard these symptoms merely as the physiologic reaction to the unhygienic mode of living now prevailing.

Pfaundler<sup>18</sup> considers the diatheses of childhood, namely, exudative diathesis of Czerny, status thymicolymphaticus of Paltauf, infantile arthritism of Comby, to represent identical conditions, viewed only from different standpoints.

#### ETIOLOGY

Friedjung<sup>19</sup> is a strong believer in Adler's theory of organic inferiority. Constitutional differences are then the reason why infants may fail to thrive under the best of care, even with well-regulated breast feeding; also why vastly different methods of artificial feeding may give either good or bad results in the hands of the same investigator.

Lederer<sup>20</sup> finds the cause of exudative diathesis in the water metabolism.

13. Czerny, A.: Die exsudative Diathese, *Jahrb. f. Kinderh.*, 1905, lxi, 199.

14. Pfaundler, M.: Kindliche Krankheitsanlagen (Diathesen) und Wahrscheinlichkeitsberechnung, *Ztschr. f. Kinderh.*, 1912, iv, (Orig.) 175.

15. v. Behring, E.: Disposition und Diathese, reviewed in *Ztschr. f. Kinderh.*, 1914, Referate, viii, 273.

16. Klotz, M.: Die Bedeutung der Konstitution für die Säuglingsernährung, Würzburg. Abhandl. a. d. Ges. d. prakt. Med., 1911, xi, 181.

17. Sittler, P.: Die exsudativ-lymphatische Diathese, Würzburg, 1913.

18. Pfaundler, M.: Zur Lehre von den kindlichen Diathesen oder Krankheitsbereitschaften, reviewed in *Jahrb. f. Kinderh.*, 1911, lxxiv, 486.

19. Friedjung, J. K.: Die Ernährungsstörungen der Brustkinder und Konstitution, reviewed in *Ztschr. f. Kinderh.*, 1913, Referate, iv, 595.

20. Lederer, R.: Exsudative Diathese und Wasserstoffwechsel, *Ztschr. für angewandte Anat. u. Konstitutionsleiden*, 1914, 1, 233.

Steinitz and Weigert<sup>21</sup> have made repeated metabolism experiments on two infants and they have found decreased nitrogen and fat metabolism.

Riesel<sup>22</sup> found that out of thirty-five children whose bodily conditions were marked on their history charts as fat or pasty, twenty-six had most of the symptoms of exudative diathesis.

Maillet<sup>23</sup> considers the subcutaneous tissue to be of the greatest importance for the nutrition as well as the defense of the body.

Mendelsohn<sup>24</sup> is an adherent of Bouchard's<sup>25</sup> theory of the retardation of metabolism and of humoral hypo-acidity.

Pässler<sup>26</sup> has a rather remarkable, though not convincing, view of the etiology of exudative diathesis. He finds this, as well as other related diatheses, to be always caused by chronic streptococcus infections of the buccal cavity, especially caries dentium and pyorrhea. He claims that thorough cleansing of the mouth will cure even eczema.

#### SYMPTOMATOLOGY

Pfaundler<sup>27</sup> states the case very clearly when he says that some children show a peculiar frequency in the disturbances of their health, no matter how carefully they are guarded against the causes which are known to produce these attacks. This proves to him conclusively that these children possess in their organisms some peculiarity in the form of a special disposition, an increased readiness towards certain disturbances, a diathesis. He differentiates the manifestations of exudative diathesis as primary, secondary and concomitant.

*Skin.*—This being the one organ which will naturally show the changes due to exudative diathesis most readily and at the same time most clearly, has therefore been studied very closely.

According to Feer<sup>28</sup> eczema is the expression of a chronic constitutional abnormality. There is no acute eczema, only acute exacerbations. Acute dermatitis is mistaken for eczema, as is proved by the

21. Steinitz, F., and Weigert, R.: Stoffwechselversuche am Säuglingen mit exsudativer Diathese, *Monatsschr. f. Kinderh.*, 1910, lxxiv, 385.

22. Riesel, H.: Adipositas and exsudative Diathese, *Ztschr. f. Kinderh., Orig.*, 1911, ii, 325.

23. Maillet, F.: Le tissu cellulaire sous-cutané dans la défense de l'organisme de l'enfant, reviewed in *Ztschr. f. Kinderh.*, 1912, Referate, iii, 319.

24. Mendelsohn: Die Frage des Arthritismus, *Med. Klin.*, 1911, vii, 752; *Deutsch. Med. Wchnschr.*, 1911, xxxviii, 857.

25. Bouchard: *Maladies par ralentissement de la nutrition*, Paris, 1882.; Bouchard: *Traité de pathologie générale*, Paris, 1900, iii.

26. Pässler: Sind die sogenannten Diathesen Konstitutionsanomalien? reviewed in *Jahrb. f. Kinderh.*, 1914, lxxix, 500.

27. v. Pfaundler, M.: Besondere Krankheitsbereitschaften (Diathesen) und Konstitutionsanomalien, Feer's *Lehrbuch der Kinderheilkunde*, 1914, Ed. 3, p. 183.

28. Feer, E.: Das Ekzem mit besonderer Berücksichtigung des Kindersalters, reviewed in *Ztschr. f. Kinderh.*, 1913, Referate, iii, 66.

results of treatment. Eczematous conditions are not skin diseases *sui generis*, but merely the symptoms of a constitutional abnormality, often in connection with external stimuli. Scrofular eczema is not the sum of tuberculosis and eczema, but through the tuberculous infection of the organism the eczema acquires a changed character which gives it its specific appearance.

Bloch<sup>29</sup> sees in the diathesis a chemical allergy. To him the diathetic dermatosis is a reaction of the allergetic skin to accidental irritation, which latter may be endogenous or exogenous in origin.

Rachmilewitch<sup>30</sup> found that slight injury to the skin followed by irritation of the same (by mustard) caused a typical reaction, not only in children with manifest exudative diathesis, but also in the latent cases, and in the new-born.

Mautner,<sup>31</sup> on the other hand, finds no difference between healthy and eczematous children in their reaction to cataplasms or to bacterial irritation.

Hirschberg<sup>32</sup> puts stress on the importance of heredity, disposition, disturbances of digestion and metabolism for the development of eczema, especially in children.

Schlesinger<sup>33</sup> found the weight of infants with universal eczema, and still more of those with localized eczema, especially during the first three months of life, to be higher than in other diseases of infancy.

Schkarin<sup>34</sup> never missed other symptoms of a constitutional abnormality in connection with eczema, such as exudations into the skin and mucous membranes, which influence the course of nutrition.

Moro and Koll<sup>35</sup> consider that the inclination to intertrigo in early infancy, to urticaria later, and to reactive inflammations at school-age are due to a lability in the vasomotors.

*Lymphatic Apparatus.*—Czerny<sup>36</sup> considers the affections in the lymphatic glands in exudative diathesis never to be primary, but always

29. Bloch, I.: Diathesen in der Dermatologie, reviewed in Deutsch. med. Wchnschr., 1911, xxxviii, 857.

30. Rachmilewitch: Hautreaktionen von Kindern mit exsudativer Diathese, Jahrb. f. Kinderh., 1913, lxxvii, 176.

31. Mautner, F.: Ueber Hautreaktion bei gesunden und ekzematösen Kindern, Ztschr. f. Kinderh., 1913, Orig., viii, 461.

32. Hirschberg, M.: Ekzem und innere Erkrankungen, reviewed in Ztschr. f. Kinderh., 1913, Referate, vii, 327.

33. Schlesinger, E.: Das Körpergewicht hautkranker, besonders ekzematöser Säuglinge, reviewed in Jahrb. f. Kinderh., 1908, lxxvii, 467.

34. Schkarin, A.: Ueber Ekzema bei Säuglingen im Anschluss an die Lehre von Diathesen im Kindesalter, Jahrb. f. Kinderh., 1914, lxxviii, 156.

35. Moro, E., and Koll, L.: Ueber das Schicksal von Ekzemkindern, Monatsschr. f. Kinderh., 1910, ix, 428.

36. Czerny, A.: Exsudative Diathese, Skrophulose und Tuberkulose, Jahrb. f. Kinderh., 1909, ix, 529.

to be secondary to pathologic processes in the skin and mucous membranes. The condition of the lymphoid organs, the thymus, spleen, tonsils, intestinal follicles, is independent of that of the lymph-glands. Their hypertrophy is due to overfeeding which favors the depositing of fat.

Benfey and Bahrdt<sup>37</sup> studied thirteen patients, none of whom had infantile eczema or tuberculosis; the clinical picture of these was dominated by adenoids and by regional glandular swellings.

*Blood.*—Kroll-Lifschütz<sup>38</sup> regards eosinophilia as a coordinated symptom of exudative diathesis.

Helmholz<sup>39</sup> and Rosenstern<sup>40</sup> both find eosinophilia accompanying eczema.

Putzig<sup>41</sup> has investigated a large material with the most careful methods and finds that healthy children have the same eosinophil count as have adults, whilst infants who later show signs of exudative diathesis have an increase in the eosinophils quite early. He concludes that eosinophilia is a symptom of exudative diathesis.

Aschenheim,<sup>42</sup> on the other hand, considers eosinophilia as a special disposition or diathesis, which is not identical with exudative diathesis but frequently combined with it.

*Respiratory Apparatus.*—Czerny<sup>43</sup> sees a great similarity in the affections of the air-passages to those of the skin. His views differ greatly from those of the French school, who consider asthma and bronchitis to be due to arthritism or herpetism, as, for instance, Goilav,<sup>44</sup> Merkel<sup>44</sup> and Spolverini.<sup>45</sup> Some children suffer from repeated affections of the same parts of the respiratory mucous membrane and in the same manner. One child has pharyngitis several times a year, another follicular angina, a third an infection of the

37. Benfey, A., and Bahrdt, H.: Beitrag zur Beurteilung der Drüzenschwellungen bei Kindern jenseits des Säuglingsalters und ihrer Beziehungen zum Lymphatismus, *Ztschr. f. Kinderh.*, 1913, Orig., vii, 481.

38. Kroll-Lifschütz, A.: Zur Frage der Eosinophilie und exsudativen Diathese, reviewed in *Ztschr. f. Kinderh.*, 1914, Referate, viii, 291.

39. Helmholz, H.: Eosinophile Blutkörperchen bei akutem exsudativem Ekzem, *Jahrb. f. Kinderh.*, 1908, lxix.

40. Rosenstern, J.: Exsudative Diathese und Eosinophilie, *Jahrb. f. Kinderh.*, 1908, lxix, 631.

41. Putzig, H.: Das Vorkommen und die klinische Bedeutung der eosinophilen Zellen im Säuglingsalter, besondere bei exsudativer Diathese, *Ztschr. f. Kinderh.*, 1913, Orig., ix, 429.

42. Aschenheim, E.: Eosinophilie und exudative Diathese, *Jahrb. f. Kinderh.*, 1912, lxxvi, 456; Ist die Eosinophilie ein Symptom der exsudativen Diathese? *Ztschr. f. Kinderh.*, Orig., 1914, x, 503.

43. Goilav: Etude sur la bronchite liée à l'herpétisme, Thèse de Paris, 1889.

44. Merkel: L'asthme chez les enfants, Thèse de Paris, 1901.

45. Spolverini, I. M.: Sulla etiologia e terapia dell'asthma essenziale nei bambini, reviewed in *Ztschr. f. Kinderh.*, 1914, Referate, vii, 221.

pharyngeal tonsil, a fourth pseudocroup, a fifth bronchitis diffusa. The different attacks are very similar, and we must therefore assume that the same local disposition exists as in seborrhea, the difference consisting only in the form of the reaction to equivalent pathologic irritation.

*Digestive Apparatus.*—Lingua geographica is according to Groos<sup>46</sup> most likely constitutional, and is found in the hereditary neuropathic type of individuals.

Lublinski<sup>47</sup> denies its connection with exudative diathesis.

Klausner<sup>48</sup> considers it congenital and consequent irritability of the mucosa of the tongue, and he states that dermatologists do not agree that it is part of the exudative diathesis.

Czerny<sup>49</sup> however regards it as one of the first symptoms of exudative diathesis, which may at times be seen during the first month of life, but only in the living child.

The appendix was examined by Lieblein,<sup>49</sup> who found considerable hyperplasia of its lymphatic apparatus and very long appendices in six young people with pronounced lymphatism.

Langstein<sup>50</sup> could not find any pathogenic organisms in many cases of infants in whose stools he had noticed pus. These infants had the clinical manifestations of exudative diathesis, and he believes that in this a special disposition to intestinal symptoms exists, which will result in mucus in the stools in light cases, and pus in the severe ones. He sees in the hyperplasia of the intestinal follicles, which was first described by Czerny,<sup>51</sup> the reason why infants with exudative diathesis react to noxae which do not affect healthy infants.

*Genito-Urinary Apparatus.*—Lust<sup>52</sup> found in the sediment of apparently normal urine which he had centrifuged, epithelium and a few leukocytes as a sign of a process of desquamation in the urogenital mucosa in more than 50 per cent. of the children with exudative diathesis.

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46. Groos, F.: Die Landkartenzunge, reviewed in Ztschr. f. Kinderh., 1913, Referate, vii, 54.

47. Lublinski, W.: Ist die Landkartenzunge erblich? Deutsch. Med. Wchnschr., 1910, xxxvi, 2343.

48. Klausner, E.: Ueber lingua geographica hereditaria, reviewed in Jahrb. f. Kinderk., 1911, lxxiv, 120.

49. Lieblein, V.: Zur Kenntniss der lymphatischen Pseudoappendicitis, reviewed in Ztschr. f. Kinderh., 1912, Referate, iii, 637.

50. Langstein, L.: Erscheinungen von seiten des Magendarmkanals bei exsudativer Diathese, reviewed in Jahrb. f. Kinderh., 1908, lxxvii, 613.

51. Czerny, A.: Zur Kenntniss der exsudativen Diathese, Jahrb. f. Kinderh., 1908, lxxviii, 513.

52. Lust, F.: Die Beteiligung der Schleimhaut des Urogenitalapparates am Symptomenkomplex der exsudativen Diathese, reviewed in Jahrb. f. Kinderh., 1912, lxxvi, 99.

Beck<sup>53</sup> in his study of forty cases of his own confirms Lust's findings of desquamative processes on the mucosa of the efferent urinary passages.

*Nervous System.*—Saenger<sup>54</sup> considers the psychic element very important as supplementing the somatic disposition of exudative diathesis.

Czerny<sup>55</sup> lays stress on the close connections between the neuropsychopathies and exudative diathesis, though he does not look on this as causative but only as a combination. Frequently the education of the child has been faulty owing to the exudative diathesis, and thus the neuropsychopathies have been favored. This explains the remarkable results which have often been observed under psychic treatment in children with intractable eczema or asthma, sometimes also in processes originating in the nasopharynx.

Pfaundler<sup>56</sup> calls the attention of physicians to cases seen frequently in which the symptoms of the lymphatic constitution are combined with those of neuropathy to form what he calls neurolymphatism. In these cases the nervous manifestations, the severity of the reflexes, are of special importance; as, for instance, the spasmodic sneezing in coryza, the pseudocroup in laryngitis, the pertussoid in bronchitis, the asthma in bronchiolitis, severe colic and mucomembranous diarrhea in enteritis, enuresis in balanitis, blepharospasm in conjunctivitis.

Czerny<sup>13</sup> explains clearly that the severity of the itching is dependent on the degree of irritability of the nervous system. The itching causes the children to scratch, and then the danger of a secondary infection and thus of an eczema is great. He warns physicians not to neglect the child's psyche over its body.

*The Eyes.*—Igersheimer<sup>57</sup> found in 70 per cent. of 152 children with phlycten a positive v. Pirquet reaction. He urges in these cases the treatment of the exudative diathesis, and he advises great care in keeping these children away from people suffering from tuberculosis.

53. Beck, C.: Die Beteiligung der Schleimhäute des Urogenitalapparates am Symptomenkomplex der exsudativen Diathese, reviewed in *Jahrb. f. Kinderh.*, 1914, lxxviii, 495.

54. Saenger, M.: Ueber die psychische Komponente unter den Asthmaursachen, reviewed in *Ztschr. f. Kinderh.*, 1912, Referate, iii, 244.

55. Czerny, A.: Zur Kenntniss der exsudativen Diathese, reviewed in *Jahrb. f. Kinderh.*, 1908, lxxviii, 634.

56. Pfaundler, M.: Ueber kombinierte Krankheitsbereitschaften oder Diathesen im Kindesalter, reviewed in *Jahrb. f. Kinderh.*, 1911, lxxiv, 601.

57. Igersheimer: Ueber die Beziehungen von Skrophulose, Lymphatismus, exsudativer Diathese zu den Erkrankungen des Auges, reviewed in *Jahrb. f. Kinderh.*, 1911, lxxiii, 271.



## METABOLISM

Menschikoff<sup>58</sup> has investigated the metabolism of children with exudative diathesis and finds that they react easier to differences in the ingestion of chlorin, increases as well as decreases, and more so with manifest than with latent symptoms.

Bernis<sup>59</sup> and Kern<sup>60</sup> look on the change in the nitrogen metabolism as characteristic. The latter found that children with exudative diathesis have a delayed excretion of uric acid.

Czerny<sup>61</sup> is convinced that the metabolism of fat is disturbed. Finkelstein and Meyer claim to have found the reason for the changes in the altered metabolism of the salts.

## CONNECTION WITH OTHER DISEASES

v. Hansemann<sup>61</sup> states that many diseases develop on the basis of either acquired or congenital constitutional abnormalities, which consist in anatomic or metabolic changes. The composition of the body fluids and the activity of the cells form the medium through which the growth of the pathologic elements may be either favored or destroyed. Some causes, like colds, or general diseases, like gout or rickets, also age and inheritance, will cause a change in the composition of the body fluids.

Unterberger<sup>62</sup> sees in the constitution a factor which is of paramount importance, especially in the development of tuberculosis, against which the action of the bacteria may be neglected.

Rozenblat<sup>63</sup> is doubtful about the connection between scrofulosis and exudative diathesis.

Czerny<sup>64</sup> clearly defines his standpoint when he writes:

The identical infectious agent does not produce similar clinical pictures in different individuals. This is due only partially to the quantity or quality of the micro-organism or its location in the body. The appearance of certain symptoms of infectious diseases and their course depends mainly on individual constitutional abnormalities. These may be either congenital or acquired; they may affect either single organs or the whole body.

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58. Menschikoff, V.: Chlorretention bei exsudativen Prozessen der Haut, reviewed in *Jahrb. f. Kinderh.*, 1912, lxxvi, 99.

59. Bernis, A. L.: Répartition de l'azote urinaire dans quelques dermatoses dites diathésiques, Dissertation, Bordeaux, 1912.

60. Kern, H.: Ueber Harnsäureausscheidung bei exsudativen Kindern und ihre Beeinflussung durch Atophan, *Jahrb. f. Kinderh.*, 1913, lxxviii, 141.

61. v. Hansemann: Die Konstitution als Grundlage von Krankheiten, *Med. Klin.*, 1912, viii, 933.

62. Unterberger, S.: Die Bedeutung der Konstitution für den Verlauf der Krankheiten, reviewed in *Ztschr. f. Kinderh.*, 1912, Referate, iii, 411.

63. Rozenblat, H.: Scrophulosis, lymphatismus, diathesis exsudativa, reviewed in *Jahrb. f. Kinderh.*, 1910, lxxii, 648.

64. Czerny, A.: Die Bedeutung der Konstitution für die Klinik der kindlichen Infektionskrankheiten, reviewed in *Ztschr. f. Kinderh.*, 1914, vii, 354.

Engel<sup>65</sup> is of the opinion that scrofulosis develops on the soil of exudative diathesis, the infection with the tubercle bacillus being added to the constitutional abnormality.

#### THERAPY

*Feeding.*—Czerny<sup>36</sup> sums up his views on the connection between exudative diathesis and feeding as follows: The idea that milk and eggs are the best food for children is erroneous, and it is most likely a relic of the days when rickets and scrofulosis were regarded as diseases due to an insufficient supply of protein in the food. The general statement that woman's milk is the best food for infants is also wrong. We can only assert that the mortality amongst children at the breast is lowest. Many children do not thrive at the breast and show all kinds of symptoms while on this food. These disturbances are due to constitutional abnormalities, of which exudative diathesis is one. Thus, for instance, seborrhea faciei is due to the feeding which brings out the exudative diathesis, and one of the symptoms of this is seborrhea. The first two years of life are of the greatest importance as concerns the appearance of exudative diathesis.

Czerny<sup>13</sup> further states that three points are of importance in the control of exudative diathesis, namely: (1) the kind of feeding; (2) the condition of the nervous system; (3) intercurrent infections. By treating this trio we can reduce the symptoms of exudative diathesis to a minimum.

Feer<sup>66</sup> believes that the congenital disposition and the mode of feeding should be considered as the causes of exudative diathesis. To fight the disposition these children must be fed sparsely; they must not get milk, butter, eggs or meat; they should have little sugar; they are allowed large amounts of fruit and vegetables.

Simpson,<sup>67</sup> on the other hand, denies the harmful effect of milk in infants with eczema, and he does not want to change the diet of the infant as long as it is thriving.

Finkelstein<sup>68</sup> is of the opinion that the relation between eczema and the mode of feeding and the gain in weight are by no means simple.

65. Engel: Die Skrophulose und ihre Behandlung, Med. Klin., 1913, ix, 2099.

66. Feer, E.: Ueber exsudative Diathese des Kindes, reviewed in Ztschr. f. Kinderh., 1912, Referate, i, 679.

67. Simpson, C. A.: Infantile eczema, Jour. Am. Med. Assn., 1912, lviii, 995.

68. Finkelstein, H.: Zur diätetischen Behandlung des Säuglings- und Kindereczems, Ztschr. f. Kinderh., 1913, viii, Orig., 1.

Steinitz<sup>69</sup> in his report from the Vegetarian Children's Home in Breslau, attributes to the diet his good results in keeping down the manifestations of exudative diathesis.

Variot<sup>70</sup> asserts that eczema is due to the "eczematogenous" qualities of mother's milk and that it may be cured by a change in the wet-nurse or in the food. Ibrahim, who reviews this paper, asks, however, why this milk was not tried on other babies who did not have exudative diathesis.

Czerny<sup>71</sup> cites a very interesting experiment which proved to him that the clinical picture, which was formerly called scrofulosis, is a combination of the symptoms of tuberculosis and of exudative diathesis.

*Climate.*—Von Planta<sup>72</sup> believes that the lessened amount of oxygen in the mountain air causes a change in the metabolism, and he therefore advises a long-continued sojourn of not less than one year.

Bockhorn<sup>73</sup> advises a sojourn of three months at the seashore for children with exudative diathesis.

*Drugs.*—Krasnogorski<sup>74</sup> proclaims himself an adherent of the theory of Eppinger and Hess, who attribute some of the symptoms of exudative diathesis to vagotomy, and he therefore recommends the administration of atropin in increasing doses.

Schreiber<sup>75</sup> has seen good results from the alkaline mineral waters, also arsenic periodically, and calcium glycerophosphate.

69. Steinitz: Ueber Vegetarismus und exsudative Diathese, *Jahrb. f. Kinderh.*, 1907, lxxv, 513.

70. Variot, G.: Beobachtungen über die Behandlung des Säuglingssekzems durch Milchwechsel, reviewed in *Jahrb. f. Kinderh.*, 1912, lxxv, 390.

71. Czerny, A.: Beitrag zur Leberthrantherapie, reviewed in *Ztschr. f. Kinderh.*, 1913, Referate, iii, 338.

72. v. Planta: Die exsudative Diathese und das hochalpine Gebirgsklima, reviewed in *Ztschr. f. Kinderh.*, 1912, Referate, i, 600.

73. Bockhorn, M.: Die exsudativ-lymphatische Diathese und die Prophylaxe, *Deutsch. med. Wehnschr.*, 1914, xl, 960.

74. Krasnogorski, N.: Exsudative Diathese, Vagotonie, reviewed in *Jahrb. f. Kinderh.*, 1914, lxxviii, 495.

75. Schreiber, G.: Les Diathèses infantiles, *Arch. de méd. d. enf.*, 1912, xv, 433.

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## THE ETIOLOGY OF TETANY—METABOLIC AND CLINICAL STUDIES \*

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Most authors who have written on the subject of infantile tetany connect the cause with a disturbance of the calcium metabolism, the greater number believing it to be due to a deficiency of calcium in the tissues. Stoeltzner<sup>1</sup> and his co-workers believe there is a stagnation of calcium in the tissues. Cybulski<sup>2</sup> and Schabad<sup>3</sup> are confirmed that the calcium excretion is not regularly increased in tetany; yet the latter finds that on giving cod liver oil and phosphorus, there is a gradual reduction of electrical irritability with simultaneously an increased calcium retention. Schwarz and Bass<sup>4</sup> failed to find any lessening of calcium retention. MacCallum and Voegtlin<sup>5</sup> observed that in parathyroidectomized dogs the injection of calcium and magnesium salts stops all symptoms of tetany and that the injection of sodium and potassium salts has the opposite tendency. In addition to this they found a reduction of the calcium content of the tissues and blood during tetany and increased excretion of calcium in the urine and feces while the tetany is developing. At the same time they found that the ammonia in the blood and urine was also increased. Rosenstern<sup>6</sup> reduced the electrical irritability by giving calcium salts in large amounts per mouth.

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1. Stoeltzner: *Jahrb. f. Kinderh.*, 1906, lxiii, 661; *Neurol. Centralbl.*, 1908, xxvii, 58.

2. Cybulski: *Monatschr. f. Kinderh.*, 1906, v, 409.

3. Schabad: *Monatschr. f. Kinderh.*, 1910, ix, 25.

4. Schwarz and Bass: *AM. JOUR. DIS. CHILD.*, iii, 1, 15.

5. MacCallum and Voegtlin: *Jour. Exper. Med.*, 1909, xi, 118.

6. Rosenstern: *Jahrb. f. Kinderh.*, 1912, lxxii, 154.

Similar use of sodium chlorid resulted in the production of electrical irritability, provided that enough was given to cause a rise in temperature. In addition to these observations he further found that the tetanoid symptoms were reduced on the withdrawal of whey from the food and conversely the symptoms were produced on the addition of it. He did not find sodium and potassium salts as effective in increasing electrical irritability as was whey containing the same amount of sodium and potassium.

Grulee<sup>7</sup> was unable to confirm Rosenstern's findings, except in regard to the experiments with whey. He introduced sodium and calcium salts by injection with negative results. However, the doses used were smaller than those employed by Rosenstern.

Finkelstein<sup>8</sup> says probably some substance in the whey is responsible for the disturbance resulting in tetany. Grulee reports a considerable number of cases of tetany in which a cure was effected by giving a food free from whey curds and barley water, with or without additional carbohydrate.

Zybell<sup>9</sup> in 1913 concluded that experimental results showed no agreement as to the effect on infants suffering from tetany, of long continued feeding of small or large doses of calcium, although occasionally one finds a slight reduction in the electrical irritability in the employment of large doses of this salt. He does not believe in any specific salt therapy.

One of the most important observations from our standpoint has been the observation by Lust<sup>10</sup> in 1913 in which he gave only a clinical report of an infant suffering from severe general edema and typical tetany. The electrical irritability disappeared with the edema. On two successive occasions the edema accompanied by tetany returned and both conditions disappeared as on the first occasion. Of equal interest is Kehrer's<sup>11</sup> report of six cases of tetany of the new-born, in two of which, the mothers suffered from nephritis with edema. Reiss<sup>12</sup> in 1911 stated that he believed that the tetanoid condition depended on the relation between sodium and potassium, on the one hand, and calcium and magnesium on the other. Grulee in further investigations was unable to demonstrate any definite variation in the salts.

Thus it is seen from previous and somewhat extensive observations that there is little uniformity of opinion. By far the greatest number of observations have been devoted towards the detection of the cal-

7. Grulee: *Arch. Pediat.*, 1912, xxix, 24; *AM. JOUR. DIS. CHILD.*, 1913, v, 205.

8. Finkelstein: *Lehrbuch der Säuglings Krankheiten*, 1909.

9. Zybell: *Jahrb. f. Kinderh.*, 1913, lxxviii, 29.

10. Lust: *München. med. Wchnschr.*, 1913, vi, 93.

11. Kehrer: *Jahrb. f. Kinderh.*, 1913, lxxvii, 624.

12. Reiss: *Ztschr. f. Kinderh.*, 1911, iii, 1.

cium, and no observations either clinical or chemical have proved any definite variations in the balance of the body salts. It might be stated in passing that the trend of opinion goes to show that the parathyroids do not play any definite part in the etiology of this disease, except in assisting generally in the metabolic processes in the body. Many autopsies have shown hemorrhages into the parathyroids, yet the cases clinically have no symptoms of the tetanoid type.

Owing to the observation made by one of us that in several cases of tetany there developed diarrhea, in the course of which the tetanoid group of symptoms spontaneously disappeared, it seemed justifiable to associate the diarrhea with the relief of the tetany. On further investigation it was found that in diarrheal stools the output of sodium and potassium may be eight to ten times that of the normal, while the change in the calcium and magnesium is but slight. Bearing this in mind, it was repeatedly noticed that when the stools of infants suffering from tetany became loose there was an amelioration of the symptoms, depending of course on the fluidity of the movements. Contrary

TABLE 1.—RATIO OF INTAKE TO EXCRETION AND PER CENT. OF INTAKE LOST IN STOOLS

	Normal Stools		Loose Stools		Very Loose Stools	
Fat .....	12.4	....	23.1	....	40.5	....
Protein .....	7.7	....	14.9	....	25.2	....
Total ash...	40.0	Urine	46.6	Urine	84.3	Urine
CaO .....	67.2	Trace	70.2	Trace	79.0	Trace
MgO .....	56.7	Trace	66.0	Trace	100.0	Trace
P <sub>2</sub> O <sub>5</sub> .....	36.9	36.7	41.4	36.0	48.3	41.7
Cl .....	3.7	79.0	17.7	70.2	52.9	17.0
K <sub>2</sub> O .....	15.4	54.9	37.9	37.9	83.7	26.6
Na <sub>2</sub> O .....	12.3	67.5	37.0	28.2	103.0	5.7

to this, it was also noted that infants afflicted with tetany, either mild or severe, were constipated and that doses of castor oil invariably produced a reduction in the patient's irritability.

At this juncture it is interesting to note what a tremendous output of salts, especially sodium and potassium, takes place in diarrheal stools and for this purpose I have reproduced the table (Table 1) from work done by Courtney and Fales<sup>13</sup> at the Babies' Hospital, New York. Here it will be observed that the output of sodium is a little over eight times the normal while that of the potassium is over five times that of the normal. The calcium and magnesium are influenced only to a much less degree.

It is a general belief, and one which has been most specifically formulated by Reiss,<sup>12</sup> that the calcium and magnesium salts act antagonistically to the sodium and potassium salts, the former tending

13. Courtney and Fales: *AM. JOUR. DIS. CHILD.*, 1915, ix, 213.

to allay nervous irritability, the latter to increase it. In other words, the formula  $\frac{\text{Na}}{\text{Ca}} \frac{\text{K}}{\text{Mg}}$  would more accurately represent the proposition. When there is a relative increase of calcium and magnesium over sodium and potassium one would expect, if we follow the reasoning on this subject, to have a decreased nervous irritability, while the opposite proposition would also be true.

From what has already been said it will be seen that no observation has yet shown any definite relation between the inorganic salts, on the one hand, and the symptomatology of tetany on the other.

It has been our object to see that if by changing the various food elements, tetany could be produced with a fair degree of certainty, and in addition to this to note if possible any change in the inorganic salts during the onset, height and curing of the condition and what substances were responsible for the ultimate healing.

Our observations have been made on a series of thirty cases of definite tetany and in addition one hundred infants who were thought to be free from tetany were carefully tested, electrically and mechanically, for any evidence of spasmophilia.

#### METHODS OF OBSERVATION

The clinical methods employed were divided into mechanical and electrical tests. Under the former classification were grouped the various irritability signs, such as Chvostek's, Trousseau's, Schultz, carpopedal spasm, laryngospasm and convulsions. The degree of intensity of each particular sign was denoted by + or + + +, etc. In this manner a fair degree of accuracy was obtained. The electrical tests were made with a galvanic, dry-cell battery equipped with a switch for reversing polarity, a rheostat for controlling the strength of the current and a balanced milliamperemeter measuring from 0.2 to 10 milliamperes.

In every instance the peroneal nerve muscle group was employed, the negative electrode being placed over the upper abdomen and the positive electrode over the peroneal nerve as it winds around the head of the fibula.

The patient to be tested is laid with feet pointing to the right of the observer whose right hand controls the positive electrode placed on the peroneal group. The left hand supports the infant's right foot in such a manner as to detect the slightest twitch occurring in the flexors of the ankle or toes. In this way slight responses are detected which would be imperceptible to the eye. The negative electrode is held in position by an assistant while the observer controls the handle of the rheostat with his elbow. It is essential that all tests should be begun with a current of sufficient strength to produce a good muscular



response, and from this point gradually reduce to a point where the slightest twitch is lost. If the reverse is attempted the lowest contraction point will be invariably passed before response occurs. It is of importance that the reading be made at the point to which the needle on the balanced milliamperemeter swings and not at its highest fluctuation.

The skin resistance varies directly with the amount of subcutaneous fat and reduces rapidly as the operation progresses, the latter fact being apparently due to the congestion developing under the electrodes, thus increasing the skin conductivity. Due allowance should be made for this individual skin resistance so as not unnecessarily to disturb the patient.

It seems to be well supported that electrical irritability may be present when one or all of the symptoms of what is called mechanical irritability are lacking; while, on the other hand, one or more of the latter may be observed without the other mechanical signs or without the electrical reaction.

The most accurate method of estimating the nervous irritability in infants is by the electrical reaction measure by a reliable machine. Escherich in 1909 definitely determined that in infants suffering with spasmophilia KOC is less than 5 ma., while AOC is less than ACC. Speaking more specifically, it requires less than 5 milliamperes of current to produce the cathode opening contraction, while the anode opening contraction is produced by less than is the anode closing contraction. Extensive observations lead us to believe that in the majority of cases of distinct tetany, KOC is not obtained less than 5, but that AOC is always reached before the ACC, which reaction may be spoken of as anodal irritability, and was found to be present in all the cases of the series; in fact in only one instance was KOC noted to be less than 5 ma.

One hundred infants were tested for evidence of mechanical or electrical irritability. Of this group there were only three instances of anodal irritability, in none of which was there a response to a current of less than 2.0 ma. None of this group showed any evidence of mechanical irritability; in other words there was nothing to suggest even a latent tetany. The type of child for control test was chosen at random on admission from a service of sixty beds treating children under 2 years of age.

A diagnosis of tetany was never made when electrical hyperirritability was the only evidence, and further, only variations of 0.2 ma. were considered significant, for below that a personal factor (susceptibility to slight twitch) undoubtedly entered into consideration.

The chemical observations were conducted on a metabolism bed slightly modified from that employed at the Babies' Hospital in New

York. The amount of food taken each day was measured and a proportionate part used for analysis. The urine and feces were collected separately. The specimens dried and ashed by Bunge's method. Sodium and potassium were separated by platinic chlorid and weighed as chlorids. The calcium and magnesium were, according to McCruden's method, weighed as calcium oxid and magnesium pyrophosphate. In cases in which only the urine was examined the amount of sodium chlorid was estimated according to Volhard's method.

#### INCIDENCE OF TETANY

From the accompanying Figure 1 it is seen that tetany occurs almost solely in the fall, winter and spring months; in other words, at a season of the year when there is no tendency towards diarrhea and

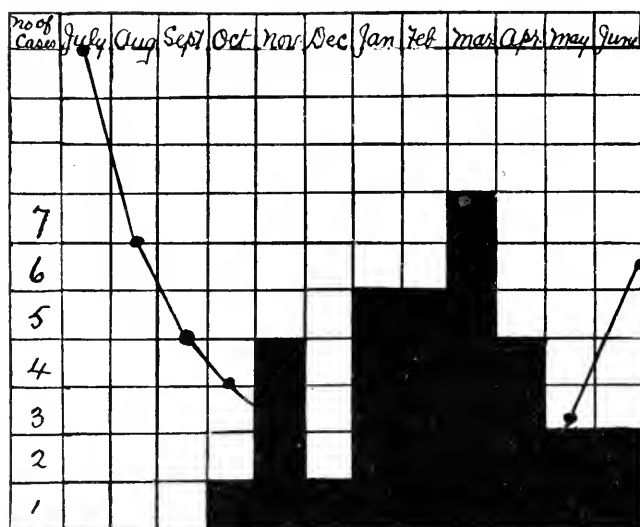


Fig. 1.—Showing monthly incidence of tetany (blocked) in comparison with mortality (curve) from diarrhea.

at which period the general inclination is towards constipation. In contrast to this, one sees no tetany in July and August, during which months the largest number of diarrheal cases occur. This may be explained by the fact that during diarrhea the inorganic salts are constantly eliminated, especially sodium and potassium, as previously noted, and hence the tendency towards irritability, from the storing up of these salts, is removed. On the other hand, during the colder months the infants tend towards constipation; hence elimination and internal combustion is less complete and we have a tendency towards a storing up of sodium and potassium, according to the nature of the food intake. Thus it is seen that the danger of tetany is removed in

the summer months, while the tendency increases at the approach of the cold season.

#### NATURE OF THE PREVIOUS FEEDING

From Figure 2 it is seen that 78 per cent. of the cases of our series of tetany occurred while being fed on proprietary and cooked foods, while 43 per cent. developed tetany on the former alone. It is worthy of note to see that five cases of the series of tetany occurred while being fed breast milk only. The remaining two cases had been fed various dilutions of pasteurized whole milk mixtures. Whether the milk had been heated beyond the 145 degrees or not it is impossible to state. Figures 3 and 4 depict the percentage of carbohydrate fed to two infants extending over a period of six weeks in one case (Fig. 3) and three months in the other case (Fig. 4); at the expiration of these

No. of Cases	Whole milk dilutions	Breast milk	Cooked foods & high carbohydrate	Proprietary foods
12				
11				
10				
9				
8				
7				
6				
5				
4				
3				
2				
1				

Fig. 2.—Showing the relation of the number of cases of tetany to the previous feedings.

respective periods each infant showed typical electrical and mechanical irritability. The average carbohydrate fed during these periods was 9 per cent., the lowest 4 per cent. and the highest 11 per cent. The fat and protein in each instance were normal for infants of their age. The only other departure from the plain milk feedings was that in each instance the food was cooked for thirty minutes. Both infants gained rapidly in weight and exhibited at the end of the periods of observation a slight degree of craniotabes. We have on record four other such cases fed in identically the same way, and in each case after a period of a few weeks exhibited, as in these two cases, typical signs of tetany and varying degrees of craniotabes.

It is an established fact that infants fed, over extended periods of time, large percentages of carbohydrates (as is contained in the proprietary foods) develop a water retention and are frequently spoken

of as "water babies." Their resistance is lower than the average child and they succumb rapidly to intercurrent infections and at the onset of diarrhea lose weight in an astonishingly rapid manner. The main increase in weight in carbohydrate fed infants is due chiefly to the fact that they are storing up in their tissues water which is in combination with sodium as sodium chlorid. Whether this ability to store water is due to the fact that the glycogen demands two molecules of water in the tissues, is not yet an established fact.

Another link in the chain of evidence of sodium chlorid retention in the tissues is the fact that when these infants lose their fluid the output of sodium chlorid is eight to ten times the normal. Infants presenting what is known as metabolism edema (due to improper

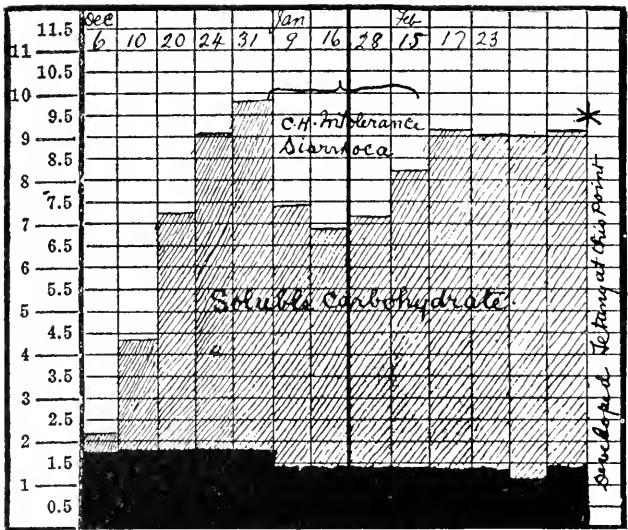


Fig. 3.—T. S. Premature infant. During a six weeks' period, following birth, fed high percentages of carbohydrates and at the end of the period developed tetany. During this period gained 3 pounds and 11 ounces.

feeding) fall into this same class, presenting definite chlorid retention, which rapidly disappears on the subsidence of the edema. In two such cases we have detected definite tetany, the symptoms of which vanished on the disappearance of the edema, coinciding with the increased chlorid output. In support of this evidence might be mentioned Kehr's<sup>11</sup> observation on five new-born infants developing tetany shortly after birth; the mothers of two of whom had nephritis with edema; and Lust's case of edema and tetany in which the tetanoid symptoms disappeared on the subsidence of the edema and recurred again as the edema reappeared.

It is thus seen that children fed on cooked foods with a high percentage of carbohydrate (as is present in the proprietary foods) show the greatest susceptibility to tetany; in other words, they exhibit a higher water content than normal infants, which water retention is chiefly in the form of sodium chlorid. The sodium and potassium ions, as previously cited, are direct excitants to the nervous tissues. Why it is that infants develop tetany on breast milk is not yet fully determined. It is possible to conceive of the fact that the metabolism of the carbohydrates of the mother's milk is incomplete in these cases, thus favoring a sodium or potassium retention, or on the other hand the total sodium or potassium content of the milk may be abnormally high. We hope to report on this in the near future.

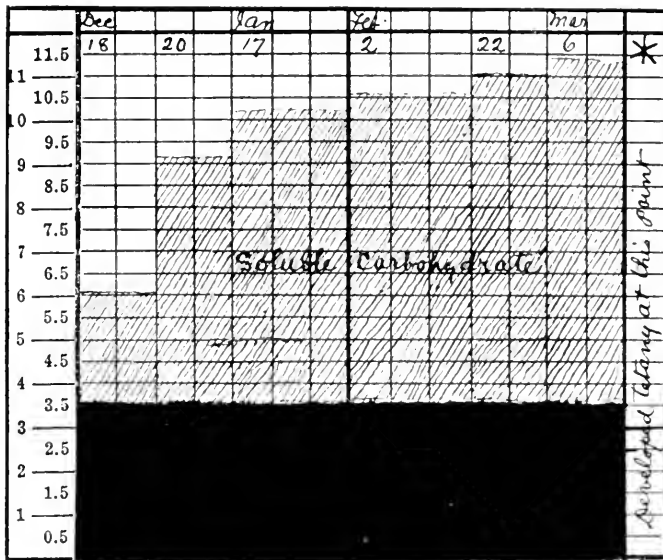


Fig. 4.—Premature infant during a three months' period following birth, fed high percentages of carbohydrates, and at the end of the period developed tetany. During this period gained 2 pounds and 11 ounces.

#### METABOLISM OBSERVATIONS

The case we have to report in detail presented an excellent opportunity for observation, first, during a period in which the symptoms were severe, and second, during a period of pronounced improvement, ultimately ending in complete cure. A preliminary report of this case with observations and comments has been made in the *Archives of Internal Medicine* by Dr. Almon Fletcher.<sup>14</sup>

14. Fletcher: Arch. Int. Med., 1915, xvi, 382.

## REPORT OF CASES

CASE 1.—G. McK., male, aged 13½ months, was admitted Jan. 7, 1915. Had been partly breast fed for nine months, supplemented with Allenbury's food and arrowroot biscuits, while for about one month previous to admission he had had Horlick's malted milk. Throughout, the child was constipated and up to the time of admission the bowel movements were obtained only by means of enemata; the stools being described as small and hard. For the last few weeks previous to his entrance to the hospital he had been cross and irritable. On December 15 he experienced a stiffening of the body accompanied by spasm of the hand and foot, characteristic of tetany. One week later a more severe attack occurred, during which time the child became cyanosed and seemed to struggle for breath. From then on similar convulsions occurred at frequent intervals until the time of admission.

Examination showed only a fairly well developed and nourished child with a moderate amount of subcutaneous tissue of diminished turgor. Enlargement of the epiphyses of the long bones, palpable spleen and a moderate degree of craniotabes were the evidences of rickets.

The child cried continuously, with occasional crowing inspiration. Feet and hands were in the typical position of carpopedal spasm. Chvostek's and Trousseau's signs were strongly positive. Deep tendon reflexes readily elicited, pronounced acetone odor on the breath. The electrical reactions showed distinct anodal irritability KCC = 0.8 ma.; AOC = 1.5 ma.; ACC = 2.2 ma.

We endeavored to approach the same type of feeding that the child had been having previous to admission, in order to eliminate as many extrinsic factors as possible, so, for this reason he was given a mixture containing approximately, fat 2 per cent.; starch 2.5 per cent., sugar 4 per cent., and protein 1.8 per cent. This combination was obtained by employing evaporated milk, 300 c.c.; barley flour, 45 gm.; lactose, 30 gm., and water, 900 c.c. This was cooked in a double boiler for thirty minutes and water added to make up the less. He was offered 240 c.c. every four hours for five feedings. A good deal of this was at first refused on account of his extreme irritability.

On January 10 he was put up in a metabolism bed and observed up to January 15. During these five days he had but three constipated movements produced in each instance by castor oil. His irritability consistently increased so that at the end of the period his electrical irritability had increased from KCC 1.0 to 0.4 ma.; AOC 2.0 to 1.0 ma. and ACC 2.5 to 1.8 ma. on the 10th. All his mechanical evidences of irritability showed a corresponding increase. Thus, as well as could be estimated clinically, his tetanoid symptoms had increased considerably, so that on the 15th he might be said to be at the height of the disease. During this period he passed very little urine, although the amount increased toward the end. See Figure 5. During this first stage of observation the child gained 300 gm. in weight.

It had been observed previously that infants fed a high protein diet, such as albumin or protein milk, had an enormous urinary output, sometimes as much as 8 to 10 times the normal. This observation led us to use urea as a diuretic which, being organic in composition, did not interfere with the inorganic estimations such as the other diuretics might have. Since these observations, however, we have found it to be much the superior diuretic for infants.

From January 16 to January 18 the infant was taken out of the observation bed and given 1.0 gm. of urea in the daily quantity of food, to stimulate diuresis, which had already begun. From January 18 to January 22 he was again put up in the observation bed. During this period a striking change occurred (see Fig. 4). The general condition improved, he took more food and seemed to be more contented. The bowels moved without the use of castor oil and seemed more free. The urine increased in quantity from an average of 182 c.c. per diem in the first period to 600 c.c. per diem in the second period.

In other words, a little over three times the amount of urine was excreted during the second period. The electrical irritability decreased from KCC 1.2 ma., AOC 1.4 ma., ACC 3 ma. on January 18 to KCC 2 ma., AOC 2.7 ma., ACC 3 ma., on January 22. The carpedal spasm entirely disappeared. Trousseau's sign could not be obtained and only a slight Chvostek sign was all that remained of the mechanical irritability. During this period there was a gain of 120 gm. Subsequently the child continued to improve and made a complete recovery.

The daily average estimations for the two periods are represented in Table 2.

From this table it is seen, in Period 1, that there is an abnormal retention of all the salts except magnesium, which, in turn, accompanied a gain in weight due to the retention of fluid. Magnesium is retained in only small amounts. In Period 2 the retained potassium has been cut in half, a daily balance of 0.4464 gm. being reduced to 0.2202 gm. The sodium retention has actually increased 0.002 gm., but the percentage of the intake retained has been reduced from 81.6

TABLE 2.—SALT INTAKE AND OUTPUT IN PERIODS 1 AND 2  
Period 1

	Intake	Feces	Urine	Loss	Balance
K <sub>2</sub> O .....	0.5460	0.0387	0.0609	0.0996	+ 0.4464
Na <sub>2</sub> O .....	0.1754	0.0194	0.0129	0.0323	+ 0.1431
CaO .....	0.4686	0.0779	0.0017	0.0796	+ 0.3896
MgO .....	0.0324	0.00761	0.02155	0.02916	+ 0.0032

Period 2

	Intake	Feces	Urine	Loss	Balance
K <sub>2</sub> O .....	0.8331	0.0770	0.5359	0.6129	+ 0.2202
Na <sub>2</sub> O .....	0.2706	0.0099	0.1157	0.1256	+ 0.1450
CaO .....	0.6948	0.2478	0.0081	0.2559	+ 0.4389
MgO .....	0.1136	0.0279	0.0149	0.0428	+ 0.0706

per cent. to 53.2 per cent. It is of equal interest to note that there has been an increase of 0.049 gm. retention of calcium while the magnesium retention has increased twenty times over that of Period 1.

The striking changes are readily seen in Table 3. Here it is to be observed that both the sodium and potassium retention in percentage of the intake has been reduced, respectively, from 81.6 per cent. and 81 per cent. in the first period to 53.2 per cent. and 26.4 per cent. in the second period. On the other hand the percentage of calcium has decreased from 83.1 per cent. to 63.2 per cent., while there has been a most striking increase in the magnesium balance from 9.8 per cent. in the first period to 62.1 per cent. in the second period.

A mere casual glance at these figures serves to show how calcium estimations alone could not account for either the development or production of tetany. The high magnesium balance is likewise noteworthy in view of its specific action on nerve tissue. This observation

alone in conjunction with those made by Berend<sup>15</sup> and Holt, Courtney and Fales,<sup>16</sup> led us to the employment of subcutaneous injections of a magnesium sulphate solution to control the irritability. So far our results have been most gratifying.

A point of most practical interest is the fact that in Period 2, 88 per cent. of the excretion of sodium and potassium was excreted by the kidneys alone, which excretion occurred simultaneously with an increased flow of urine. In the first period, when the alkalies were retained, the kidneys were remarkably inactive. This observation has been of practical value, for, as will be shown later, the estimation of the sodium chlorid content of the urine alone is of decided diagnostic and prognostic import. In addition it offers a safer method than the production of diarrhea, to rid the body of the offending alkalies.

TABLE 3.—SALT RETENTION, ETC., IN PERIODS 1 AND 2

Period 1			Period 2		
	Retention in Grams	Percentage of Intake Retained		Retention in Grams	Percentage of Intake Retained
K <sub>2</sub> O .....	+ 0.4464	81.0	K <sub>2</sub> O .....	+ 0.2202	26.4
Na <sub>2</sub> O .....	+ 0.1431	81.6	Na <sub>2</sub> O .....	+ 0.1450	53.2
CaO .....	+ 0.3896	83.1	CaO .....	+ 0.4389	63.2
MgO .....	+ 0.0032	9.8	MgO .....	+ 0.0706	62.1

The association of suppressed urine and constipation in tetanoid infants is most common; in fact in every one of our cases in which we obtained reliable information, either one or the other and frequently both were prominent symptoms. The association of fluid retention and gastro-intestinal disturbance (constipation) observed in the first period is seen not infrequently in children and the former seems to depend directly on the digestive disturbance, since observation has shown that it can be controlled by changes in the diet and disappears as an improvement in the digestion or general metabolism occurs.

#### CLINICAL OBSERVATIONS

These observations we have divided into four groups:

1. Showing the effects of diuresis.
2. Showing the effects of purgation.
3. Showing the effects of cod liver oil and phosphorus.
4. Showing the effects of a combination of the above three methods.

15. Berend: *Monatschr. f. Kinderh.*, 1913, xii, 269.

16. Holt, Courtney and Fales: *AM. JOUR. DIS. CHILD.*, 1915, ix, 318.



It must be borne in mind that all the severe cases received one or more doses of magnesium sulphate in order to tide them over the danger period and to enable the instituted treatment to exert some influence in lowering the irritability and thus remove the patient from the danger zone, when the injections were stopped. A detailed report of these injections will be presented at a later date.

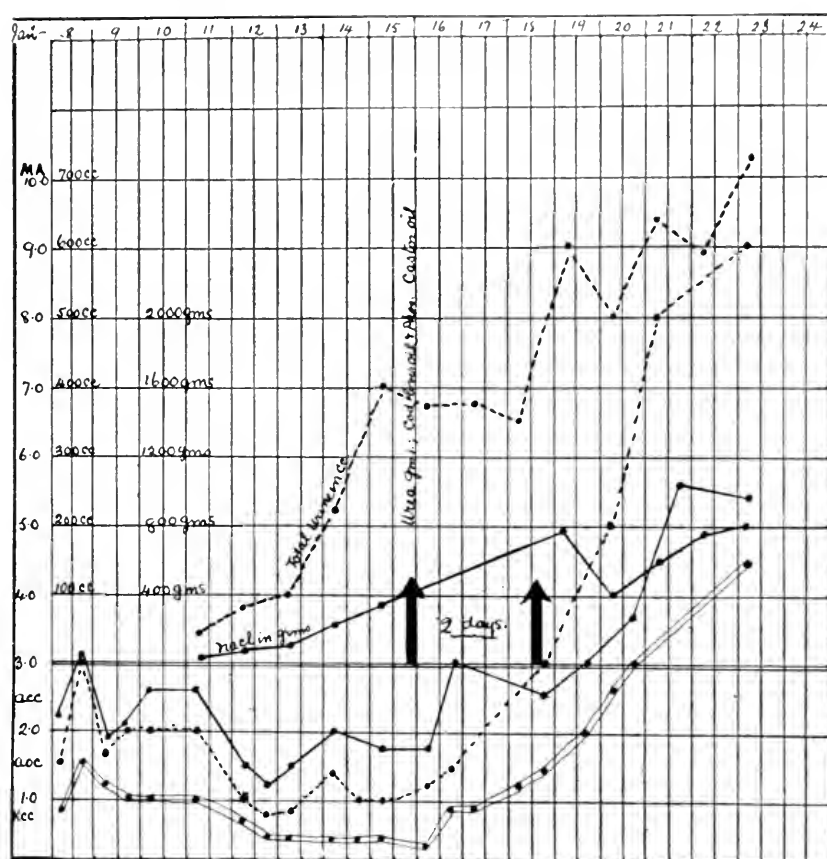


Fig. 5.—Case 1. G. McK. Showing the disappearance of the tetanoid symptoms accompanying the increased urinary output and sodium chlorid excretion.

#### Group 1: Effect of Diuresis

CASE 1.—G. McK., aged 13 months, admitted January 7. This case has already been referred to under metabolism observations. A brief reference to Figure 5 shows the increasing irritability accompanied by kidney inactivity, and vice versa, at the commencement of increased kidney secretion, which began without a diuretic two days previous to the institution of treatment, but was augmented on the administration of 1 gm. of the organic diuretic urea and 6 c.c. of castor oil. Two days following the commencement of treatment there was complete loss of all irritability which did not again recur. The chlorids had

increased from 0.025 gm. in twenty-four hours to 0.622 gm. at the time of the loss of irritability, a total increase of 96 per cent. over the excretion on admission. As the child improved the chlorid excretion increased until two weeks following cure it was found to be approximately 200 per cent. more than on admission, when the irritability was at its highest. At the time of the administration of urea, cod liver oil and phosphorus treatment was commenced, with the idea according to Schabad's observation, of increasing the calcium retention. It should be noted that observations with the administration of cod liver oil and phosphorus show that there is practically no change in the calcium

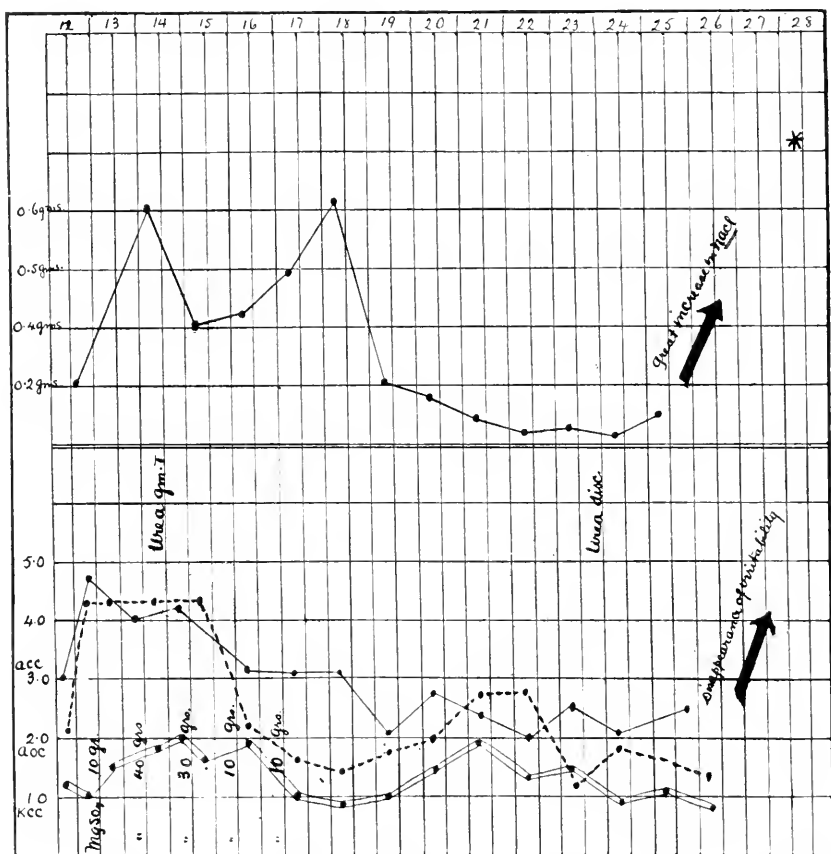


Fig. 6.—Case 2. W. S. Comparing the electrical irritability with the sodium chlorid excretion.

retention till a period of about ten days or two weeks has been reached, so it is obvious that its administration had no effect on the rapid cure of this patient, but undoubtedly aided in the permanent healing which resulted. This plan has been followed more or less in all of our observations.

CASE 2.—W. S. (Fig. 6), aged 5 weeks, admitted Jan. 11, 1915, showed pronounced electrical and mechanical irritability. No treatment other than urea was instituted, except subcutaneous injections of magnesium sulphate solution to control the convulsions. Under the exhibition of urea, curiously, the chlorid excretion dropped from 0.235 gm. to 0.075 gm. over a period of nine days; it

was then discontinued and small doses of cod liver oil and phosphorus commenced. In ten days' time the chlorids had reached 0.822 gm. per day, this being coincident with a loss of all irritability as indicated on the chart. This phenomena has been occasionally observed, namely: after the discontinuance of the urea the chlorids increase. We do not think in this instance either that the cod liver oil could have had any such effect, as it was given only in 20 minimum doses, and the response was too rapid. It will be noted on reference to Figure 6 that at the period during low chlorid excretion the irritability was at its height.

CASE 3.—J. S. (Fig. 7), aged 15 months, was admitted April 13, 1915, with edema of face and extremities, in addition to which there were pronounced signs of tetany, including extreme electrical irritability. The child was given a plain milk and water mixture and put up in the observation bed. Unaided

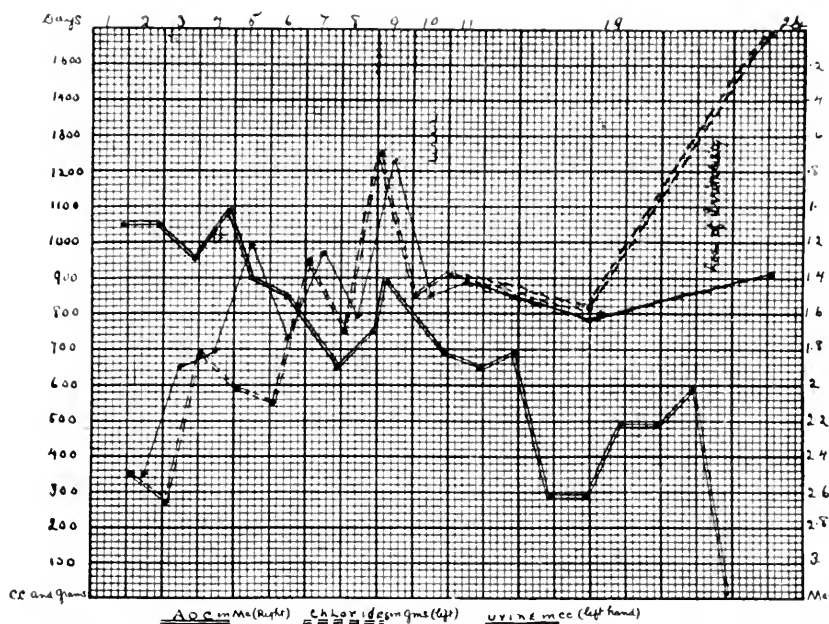


Fig. 7.—Case 3. Comparing the electrical irritability with the sodium chlorid excretion.

a diuresis immediately set in to such an extent that at the end of two weeks he had lost 1,060 gm. in weight, during which time his edema gradually disappeared. The changes that occurred at the same time were, (a) gradual reduction in his irritability, and (b) gradual increase in the sodium chlorid excretion. On admission he was found to be excreting 0.342 gm. in all the first day, and 0.258 gm. the second day; the output gradually rose till eight days following admission when he excreted 1.364 gm. in twenty-four hours or an increase of nearly five times the output at the height of the irritability. In this instance urea had practically no effect in increasing the urinary output as it had already begun and was well established when the diuretic was added. Throughout, the stools averaged one to two a day and were well digested. At the height of the chlorid excretion cod liver oil and phosphorus were given in 3 c.c. doses three times a day which completed the cure twenty-three days following admission. This child then exhibited a tremendous chlorid retention

as manifested by his edema, and later the loss of chlorids. At the height of the edema the tetany was at its worst, the signs disappearing as the chlorids increased.

*Group 2: Effect of Purgation*

CASE 4.—W. E., aged 6 months, was admitted for convulsions and found to have pronounced mechanical and electrical irritability. During a period of one week the irritability remained practically unchanged with no treatment; at the expiration of this time the child developed a severe diarrhea with seven to eight watery stools a day. In forty-eight hours there was complete absence of all the tetanoid group of symptoms. Many other instances might be cited, only not to such a striking degree. So convinced are we that we do not fear the onset of tetany as long as the bowels are moving freely.

*Group 3: Effect of Cod Liver Oil and Phosphorus*

To this group belong the cases whose symptoms are not severe and in which it is safe to wait a period of ten days or two weeks before any curative results may be expected.

CASE 5.—F. M., aged 15 months, was admitted April 9, 1915, with fairly pronounced mechanical and electrical tetany. The child was given a diet consisting of whole milk, cereals, beef juice and fruit juice and at the same time 3 c.c. of cod liver oil and phosphorus three times a day. In one week the irritability had slightly diminished and at the end of the following week had entirely disappeared. Throughout, the digestion remained perfect and the stools averaged one a day. The anodal irritability on admission was 1.2 ma., at the end of the first week, 2.8 ma., at end of the second week greater than 3 ma. with no mechanical signs of tetany.

CASE 6.—E. G., aged 8 months, was admitted March 8, 1915, and given a plain milk and water mixture in addition to 1 c.c. of cod liver oil and phosphorus three times a day. The child was suffering from a moderate degree of tetany, the anodal irritability being 2.5 ma. At the end of six days there was a slight increase to 2 ma. The medication was increased to 2 c.c. three times a day. In four more days there was complete loss of all mechanical and electrical irritability.

*Group 4: Effect of a Combination of all the Above Three Groups*

By this we mean an initial dose of castor oil to clear out the intestinal tract, the administration of urea and cod liver oil and phosphorus. To this group belong the most dangerous and severe type of cases, our idea being primarily to eliminate as much as possible of the stored up sodium and potassium in the feces by purgation, and to continue this elimination by activating the kidneys through the exhibition of urea and then endeavoring to increase the calcium retention through the administration of cod liver oil and phosphorus.

CASE 7.—H. T., aged 6 months, admitted Feb. 2, 1915, with a history of spasms extending over two months, showed pronounced electrical and mechanical irritability, in fact, the child was on the verge of convulsions. Both the mother and nurse volunteered the information that during the past few days the patient had passed very little urine. The infant was immediately given a dose of castor oil to relieve the constipation, urea gm. 1 in the total days' food, which consisted of protein milk, and at the same time cod liver oil and phosphorus 1.5 c.c. three times a day. For the first three days injections of magnesium sulphate were given subcutaneously to control the spasms, which as previously mentioned, were very severe. In three days following admission there was a decided reduction in both mechanical and electrical irritability, and in six days the AOC had risen from 1.2 ma. on admission to 3 ma. There was complete loss of all irritability on the tenth day. The child went on to complete recovery. Although the daily quantity of urine was not measured, a close watch was kept, the nurse in charge reported a great increase in the

urine after the first twenty-four hours which continued as long as the urea was administered.

CASE 8.—M. S., aged 9½ months, admitted March 2, 1915, suffering from severe convulsions over a period of two weeks, showed on examination severe mechanical and electrical irritability. The same treatment was instituted as in Case 7 of this group. After the first twelve hours there were no more convulsions and on the third day there was a slight reduction in the electrical irritability. On the thirteenth day there was a decided reduction, the AOC having risen from 1.2 ma. on admission to 2.5 ma. Two days later there was complete loss of both mechanical and electrical irritability. The child made a complete recovery.

In these two cases the symptoms had lasted over a period of from two weeks to two months, during which there was ample opportunity for the establishment of a severe salt disturbance, which was evidenced by the convulsions and severe spasms in each case. In both a cure was effected within two weeks from the institution of treatment, and in each case the healing was permanent. All avenues of excretion were utilized and the retention of the sedative salt increased through the administration of cod liver oil and phosphorus.

#### SUMMARY

An extensive review of the literature reveals the fact that there is little uniformity of opinion as regards the etiology of tetany. Most authors who have written on the subject have associated the disturbance with a lack of calcium in the system and only one author has suggested the possibility of a general salt disturbance, but has cited no definite proof. Metabolism observations on patients suffering from diarrhea reveals the fact that in severe water loss through the bowel the output of sodium and potassium is eight to ten times the normal.

The production of tetany is probably due to the fact that the organism has been storing up fluid in the tissues, which fluid is in combination with sodium and potassium salts. This phenomena is brought about by the feeding of improper foods composed of high carbohydrates which have been subjected to heat. The association of fluid retention and gastro-intestinal disturbances (constipation) is seen not infrequently in children, and the former seems to depend directly on the gastro-intestinal disturbances, since observations have shown that it can be controlled by dietetic changes, and disappears as the digestion improves.

As previously mentioned, carbohydrate and the salts of sodium and potassium are especially liable to induce these changes and may well be reduced when there is any reason to believe that fluids are being retained. Taking away part of the whey from the food, as is sometimes done in the treatment of tetany, is a means of lowering the sodium and potassium intake; the calcium remains in the curd.

Apparently the sodium chlorid estimation in the urine is an index of the irritability, and as the kidney function improves the irritability lessens or disappears. The production of diuresis is a much safer method of elimination than that of purgation. Undoubtedly calcium estimations alone do not account for the nerve irritability in tetany, but would seem to support the hypothesis that the tetany results from a disturbance of the concentration equilibrium of the salts and such salt changes are probably associated with gastro-intestinal disturbances and decreased flow of urine, and, as improvement in the function of these two systems occurs, restoration of the normal salt equilibrium ensues.

#### CONCLUSIONS

1. Tetany may be produced by high carbohydrate foods which have been subjected to heat up to or over the boiling point.

2. The monthly incidence of tetany is probably due to a disturbance of the gastro-intestinal tract (constipation), decreased internal combustion and the comparative safety from diarrhea in feeding high carbohydrate foods during the cold months.

3. A diagnosis of tetany is suggestive when there is manifest kidney inactivity in constipated infants fed heated foods of high carbohydrate content.

4. As a result of this improper feeding there is produced a disturbance of the body salts. At the height of the disease there is an almost complete retention of sodium and potassium (the irritating salts) and a great loss of magnesium. As improvement ensues there is an increased flow of urine accompanied by a relief of the constipation, during which the stored up sodium and potassium are rapidly lost.

5. This salt disturbance may be remedied first by purgation, second by diuresis, third by the administration of cod liver oil and phosphorus to build up the calcium content, and fourth by a change of diet.

6. The severe spasms or convulsions may be temporarily relieved by subcutaneous injections of a solution of magnesium sulphate.

We wish to express our thanks to Dr. R. I. Harris for the chlorid estimations, to the nurses, and to Drs. Smith and Binkely of the house staff for their hearty cooperation.

440 Avenue Road—532 Huron Street.

## A CONTRIBUTION TO DUCTLESS GLAND THERAPY \*

ROYAL STORRS HAYNES, M.D.

NEW YORK

The contribution which I have to make has to do with the action of the pars intermedia of the pituitary gland. These particular activities of the gland, from a therapeutic standpoint, have become apparent through a study of an abnormal child carried on for the past two and a half years by me, and previously by several physicians connected with the dispensary of the Babies' Hospital, including Drs. Kerley and Van Ingen.

The patient was seen first on Sept. 1, 1905, at the age of 3 years and 8 months, when a diagnosis of cretinism was made on a history that she did not walk nor talk and on the presence of coarse, thick hair, an open mouth, a lolling tongue, short thick thighs, a fontanel of  $1\frac{1}{2}$  by  $1\frac{1}{2}$  inches and a weight of  $27\frac{1}{2}$  pounds.

Given thyroid in small doses, she gained rapidly and steadily in weight and height and intelligence. In seven months she was walking and talking and was regarded as very mischievous. At the end of two years' treatment she was bright and intelligent with a closed fontanel and a not greatly protuberant abdomen. Enuresis was noted toward the end of this period.

Shortly after this it was noted that she was not so bright and the dose of thyroid was increased somewhat. She wet the bed a good deal and her skin had a tendency to break out and to be rough. Still she made good progress in weight and height, reaching  $45\frac{1}{2}$  inches at 8 years (January, 1910) and  $56\frac{1}{2}$  pounds.

At this time she came under the direct charge of an assistant who was an enthusiast who regarded her slowness in mental progress as an evidence that she needed more thyroid, and who proceeded to increase her dose successively from 3 grains a day, the maximum up to then, to 4, 6, 9, 10 and even 15 grains of B. W. & Co. thyroid a day. She had 10 grains a day during the entire year 1912.

This increase of thyroid was not productive of mental improvement, and it did result in an immediate loss in weight and a subsequent development of signs of hyperthyroidism already foreshadowed, perhaps in the enuresis and tendency to rashes, particularly scabs about the nose. She became nervous, irritable, of a poor memory, wet the bed every night and the mentality became even duller.

When she came under my direct care in February, 1913, she was 11 years old, a large child, a little shorter than the average, and a little above average weight. She was dull in school and could not pay attention. She wet the bed every night. She was very nervous and irritable, and had an ugly temper. Her nervousness had reached such a degree as to amount to a positive tremor which had been suspected to be chorea. This prevented her using pen and ink. Her appetite was excessive—she ate all the food that she could lay her hands on—one morning she ate eight rolls for her breakfast.

Her pulse was 120. There was no heart murmur. She weighed 73 pounds and measured in height  $53\frac{1}{2}$  inches in stockings.

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\* Read at the meeting of the American Pediatric Society, Lakewood, N. J., May, 1915.

It was apparent that she was suffering from too much thyroid, as both the dosage and her symptoms showed. It was decided to omit the drug for a time, instead of merely diminishing the dose. This the mother consented to do, although a little reluctantly, because she had been instructed never to let any one stop giving the child thyroid.

By the next visit we had been rewarded by one dry night and steadier nerves. In a month she had wet only three nights. In six weeks, she was not at all nervous, and did not wet at all. Her weight had increased 10 pounds in this interval.

Because her color was grayish, and because it was feared that some injury might follow too long withdrawal of the thyroid, she received  $2\frac{1}{2}$  grains (now known to be plainly too much) for two weeks. She wet the first night it was resumed and in two weeks had lost weight. Thyroid was again withdrawn and kept withdrawn until the fall of 1913.

During the spring and summer of 1913 she improved rapidly, becoming much brighter in school, less irritable, livelier in disposition. She began to pay attention to things she had never noticed before, such as remarks made around her. She learned to read and could no longer be fooled by spelling out words. She began to write with pen and ink, which she could not do before because of tremor.

Her appetite became normal, and while still very good, it was quite easily satisfied. Bed wetting became a lost art.

Along with her remarkable gain in weight, which will be noted on the chart, was the development of the breasts, first noted in June, 1913, and a little hair on the labia. She seemed remarkably normal in every way except that she showed some of her cretinism in her shortness, her lordosis and her prominent abdomen.

In September, 1913, occurred another attack of poor appetite and grayness such as had occurred a month after withdrawal of thyroid. This disappeared promptly with calomel and rhubarb and soda, without thyroid.

However, later in the fall, an attempt was made to improve her condition of slowness, which seemed to be increasing, by giving a preparation of thyroid gland made by Dr. Kendall, then working at St. Luke's Hospital. It was noted that she had become a heavy sleeper, difficult to rouse. She was slow in her motions, which may have had some relation to her greatly increased weight. Her skin was thickened with what looked like the thickness of myxedema, but her color was good and her expression intelligent. Dr. Kendall's preparation "B" was supposed to affect particularly the skin and the intelligence. She had this seventeen days, when the supply ran out and no more could be obtained, as a lot of thyroid obtained from a large pharmaceutical house gave a "B" which was quite inert. This was attributed to bacterial action in improperly kept glands. This drew my attention to the necessity of having absolutely fresh glands and immediate desiccation.

In January, 1914, she began to show definitely the symptoms which we came to call "acromegaly."

During the whole of the preceding six months, at least, it seemed that some other agency had been set at work or released by the withdrawal of the thyroid, because her weight had increased so rapidly and her general bigness, although her height had not.

She now had gained 10 pounds in four months, and almost nothing in height. She looked very chunky; her face was of a heavier cast; she looked older and sullen. Her hands were broad and the fingers blunt. To investigate the possibility of pituitary involvement, her wrist and her head were radiographed and her tolerance for glucose determined.

The sella turcica was enlarged, the antero-posterior diameter being 14 mm.; the depth 9 mm. (Normal adult of same size head A.P. 10.8, D. 7.7.)<sup>1</sup>

1. Potts: Jour. Am. Med. Assn., Sept. 27, 1913, p. 1188.



The wrist seemed practically normal for her age, which was surprising considering her cretinism.

By mistake, when we came to test her tolerance for glucose, she received 250 gm. instead of 150 gm. Yet she retained it, showing no glucose in the urine.

Acting on the assumption that an increased tolerance for glucose meant a deficient pars intermedia secretion, we concluded, rightly or wrongly, that there was a hyperplasia of the pars anterior causing enlargement of face, hands and feet, and that this might have, by pressure on the pars intermedia itself, or its blood supply, caused its secretion to become deficient. This hypothesis is strengthened by analogy with the pituitary of pregnancy, and by Cushing's statement that an enlarged anterior lobe may exert pressure on the posterior lobe, disturbing its secretion. It was determined to act on this.

A preparation of pars intermedia was obtained in capsule form, each capsule being the equivalent of 150 pounds of live bullock. This preparation has the merit of being dried and made stable within forty-five minutes of the removal of the pituitary from the slaughtered animal. It is mixed with milk sugar and will keep in the cold a year. There is no pars posterior (*nervosa*) included in the preparation.

Before this was administered, a photograph (Fig. 1) was taken showing the child about March 20, 1914. This shows pretty well her peculiar appearance. She looks more like a little ugly young woman than a child of 12; her face is heavy. The squareness of her figure is accentuated by the prominence of her bust. Her skin was thick and solid, particularly over thighs, buttocks and abdomen. Her complexion had taken on a yellow cast. The skin around her finger nails was scaly, and the skin generally was rather cold and not pleasant to the touch.

She was slow in her motions; a heavy sleeper and hard to waken. She was eager to play, but much slower than other children. She seemed to be learning music, which she loves, and was very apt at learning all the modern dances which she dances well. She was clever with her needle and could trim hats. School work did not go very well. She weighed 106½ pounds and was 54½ inches tall.

After two weeks of capsules, it was noted that the expression was brighter, as if something had lifted from her countenance; her mouth was more closely shut and she said "Hello" briskly when she entered the office. More noticeable was the increased smoothness of her skin and its thinning, which enabled one to pick it up easily, which could not be done previously.

In a month her face had lost its vacant, sullen look. Her skin had improved. She seemed more slow than ever about getting up and about. This may have been due to her increased weight, which had gone to 108 pounds. This increase may have been due to successive attempts to test her tolerance for glucose, which usually resulted in vomiting. Later it was noticed that the weight increased noticeably after these ingestions of glucose—more than the weight of the ingested glucose.

The capsules were continued. By July it had been noticed that in addition to the change in facial expression and skin, there had been a distinct change in the contour of her hands. The fingers became tapering where they had been blunt, distinctly more pleasing to the eye and the touch. Her hips were more slender and shapely; the lower extremities were straighter and the ankles could be brought closer together. The skin was soft and the hair more oily. Her breasts were larger, there was more pubic hair, but no menstruation. Her complexion was pink and white. She had become quick at repartee, but was still a heavy sleeper and routine school work was difficult.

By October she had improved a little in waking. The use of adrenal for two weeks did nothing, while the omission of the capsules of pars intermedia caused a return toward a yellowness and roughness of the skin. She was still slow on initiative, and it was determined to introduce thyroid without the capsules to see its effect.

After three weeks on thyroid gr. 3 to gr. 1, she had lost 3½ pounds; her skin was drier, and her hands a little more blunt, but she seemed keener intellectually, got up of her own accord and had become very talkative.

Pituitary was resumed, 1 capsule and gr. 1 of thyroid, and continued until Feb. 24, 1915, a steady improvement taking place in skin, contour—the hips were very slender and for the first time in a long while she could put on and button an ordinary shoe without setting the buttons over. A photograph was taken then because it was determined to stop the pituitary while continuing the thyroid to see if the *pars intermedia* was really necessary.

Mentally she had become more alert—she had become an expert dresser, although precipitate in undressing; was fond of reading—such books as the "Five Little Peppers" and the Alger books. She was very inquisitive, and clever enough to be away at dish-washing time. Had become conscious of self—began to care what she had to wear and show some speculative faculty. She said once: "I wonder what I would have been if I hadn't gone to him" (the writer).

Pituitary was omitted until April 13, six weeks, and then a third photograph was taken. While well and retaining her improved figure, there was a certain heaviness of face that had crept into her look and her complexion was yellower, her skin rougher on back of arms, thighs and buttocks. Her fingers were a little blunter. She was slow in her movements.

This experiment was particularly interesting, because when she came to see me on March 16 I had not ordered her to stop pituitary, but contemplated doing so at that visit. When I saw her, I thought she was sick and immediately gave up the idea of doing so. It transpired that the undoubtedly more sullen expression, the yellowness and the thickened face, was due to her mother having stopped the capsules according to what she thought I had directed two weeks before. I felt my judgment sustained by this accident.

Since this time she had had one to three capsules a day and there had been marked and rapid improvement again, in all the characteristics which seem to be affected in her by the pituitary. There has been general improvement in color, clearness, whiteness and smoothness of skin, which feels warm and pleasant to the touch. Even around the nails it is good.

The changes in symmetry are particularly noticeable, as before when taking capsules, the slope of shoulders, slenderness of waist, slenderness of hips, thighs, legs and ankles and straightness of lower extremities. There is less protuberance of abdomen and her lordosis is less marked. The hands seem lower down toward the knees. Her sisters think she has grown taller, but it is only an inch.

To any one who has seen her, she does not appear to be an abnormal child, only a rather heavy, stocky one, very good natured and not sensitive to pain.

Miss Keller, who tested her for intelligence by the Binet-Simon card, remarked on her wonderful complexion.

Her blood pressure now is 160 systolic, diastolic, 70; pulse rate, 72.

She still has a tolerance for 150 gm. glucose.

Her blood sugar (which Dr. Schloss was good enough to determine) is 0.58 per cent.; 3½ hr. p. c.

Her intelligence registers about 9 years, but this is to be qualified by the possibility of an imperfect pedagogic method, inasmuch as she does not attend a special school.

Roentgenogram of sella May 19 shows A.P. 15 mm., D. 9 mm. (this may be distorted).

Roentgenogram of wrist now shows the pisiform.

Photograph, Figure 3, speaks for itself. She has not menstruated.\*

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\* Menstruation appeared in June, 1915, was profuse, continued a week and was accompanied by a fair amount of pain.

A provocative injection of 0.5 c.c. pituitrin (P. D. & Co.) into the subcutaneous tissue of the right arm following the ingestion of two capsules and 150 gm. glucose produced a faint trace of sugar in the first six hours' specimen following injection.

It seems evident in this case, that, assuming a deficiency of thyroid as evidenced by the condition when first coming for treatment, there is also an affection of the pituitary; that this affection of the pituitary partakes of the nature of a deficiency of the pars intermedia, whether or not one is ready to assume an overgrowth of the pars anterior, and that the exhibition of pars intermedia has improved the condition in unexpected ways.

The questions of whether the pituitary has always been at fault, or whether the overdosing with thyroid has affected it, or the withdrawal of thyroid has simply allowed it to assume an activity, are subjects for pleasurable speculation. I cannot feel certain about it, although as the pituitary symptoms developed, it looked as if they came out from behind a withdrawing curtain of too much thyroid.

It seems evident, also, that the hypothesis on which pituitary medication was started has, as I have indicated, some probability.

The secondary sexual development would seem not to be due to pituitary directly, but to the effect of disturbance of that gland on the interstitial cells of the ovary, known to be closely associated with the pituitary.

There are no neighborhood symptoms and no evidence of tumor.

The effect of thyroid during the past three years seems to have been confined, so to speak, to setting the pace for her initiative, and also in clearing up the scaly skin about the finger nails, although before thyroid was resumed, there was some evidence of benefit in both these conditions under pars intermedia.

The effect of the pars intermedia on the mentality was no less striking than it was unexpected. Perhaps we should say "on the disposition," for the intellectual changes took place to a large degree simply from withdrawal of thyroid, and its present continued low standard may be due somewhat to the child's being in a graded class. However, in liveliness of disposition, sweetness of temper, general interest in things, and a sense of personality, the pars intermedia therapy has seemed to have great effect.

It has been remarkably interesting in following the unfolding of this case to see

1. Symptoms which might rationally have been considered to be due to hypothyroidism clear up with the exhibition of pars intermedia;
2. The remarkable effect which the exhibition of this lobe had on the smoothness, texture, and color of the skin and its warmth;

3. The striking changes in contour of hands, ankles, hips, shoulders, thighs, buttocks, etc., changes which could be made to come or to recede with the giving or taking away of the gland.

I am aware that in the consideration of this case we have come but part of the way, and that it will be necessary to investigate other glands before a final conclusion can be reached. It has taken me a year to determine to my satisfaction the value of and the necessity for the pars intermedia and the essential slowness of the method must be my apology for any incompleteness.

#### CLINICAL NOTES

F. L., aged 3 years 8 months. Family history negative. No miscarriages. Whooping cough previously. Nursed ten months. Now having general table food.

Sept. 1, 1905: Brought to Dr. Kerley's Clinic at Babies' Hospital Dispensary because baby does not walk or talk. Hair coarse. Thighs thick and short. Mouth open. Tongue out. Diagnosis, cretinism.

September 6: Fontanel  $1\frac{1}{2}$  by  $1\frac{1}{2}$ ; weight, 27 $\frac{1}{2}$  pounds. Having thyroid extract  $\frac{1}{4}$  tablet (? amount) t. i. d. Baby sleeps better.

September 13: Uses eight more words than she did. Is more playful and brighter. Stools normal. Weight, 28 $\frac{1}{2}$  pounds.

September 20: Increasing in disposition to talk. Plays better, but seems somewhat restless. Thyroid  $\frac{1}{4}$  tablet b. i. d.

September 27: Vocabulary increased by four or five words. Still a little restless. Bowels more regular. Mother thinks child much brighter. Speaks about thirty words. Weight, 28 pounds.

October 4: Had an attack of vomiting and diarrhea; mental condition shows no change. Thyroid gr.  $\frac{1}{2}$  b. i. d.

October 18: Vocabulary increasing. Seems brighter. Continue treatment with addition of lard innunctions and salt baths. Weight, 28 pounds.

November 1: Doing well. Weight, 28 $\frac{1}{2}$  pounds.

November 15: Much brighter. Puts two words together. A little constipated.

November 22: Yesterday used four words together. Weight, 29 $\frac{1}{2}$  pounds.

December 13: Improving steadily. Talks much more fluently. Fontanel,  $\frac{1}{2}$  by  $\frac{1}{2}$  inch.

Jan. 17, 1906: Aged 4 years, December 30. Adenoids and tonsils taken out at 3 $\frac{1}{2}$  years. Is still improving, though more slowly. Words are spoken quickly. Tongue protrudes less. Is brighter and more cheerful. Still constipated. Thyroid to be gr.  $\frac{1}{2}$  t. i. d. Weight, 31 $\frac{1}{2}$  pounds.

March 28: Walks, talks, plays and is very mischievous. Fontanel closed. Tongue in mouth. Mouth still open a little. Legs are straightening. Weight, 32 $\frac{3}{4}$  pounds. Height, 35 $\frac{1}{2}$  inches.

November 23: Tongue is not large. Teeth are poor. Legs are almost straight. Liver and spleen are not felt. Is bright and intelligent. Abdomen is much less prominent. Fontanel closed. Much incontinence. Atropin gr. 1/200 ON OM. Weight, 39 pounds. Height, 38 inches. A. S. S. to internal malleolus, 17 $\frac{1}{4}$  inches. Acromion to tip middle finger, 14 inches. Circumference head, 21 $\frac{1}{8}$  inches. Circumference chest, 21 $\frac{1}{2}$  inches. Circumference abdomen, 20 inches.

Jan. 16, 1907. Continue treatment. Height, 38 inches.

September 20: Height, 39 inches.

November 20: Much improved in the past three months. Talks better. Is brighter. Teeth very bad. Height, 40 inches. Weight, 48 $\frac{1}{2}$  pounds. Circumference of head, 22 $\frac{1}{2}$  inches.

July 11, 1908: Doing fairly well, but mother thinks she is not quite so bright. Increase thyroid from gr.  $1\frac{1}{2}$  to 2 a day. Still is constipated.

October 7: Goes to school. Seems to be in very good condition. Height, 42 inches. Circumference of head,  $22\frac{1}{2}$  inches.

Jan. 20, 1909: Had measles. Thyroid was stopped for one week. Was very dopey after one week without thyroid. With resumption of thyroid picture cleared up. (A later story tells that child had very severe measles and was practically comatose during it and the physician in attendance regarded the withdrawal of thyroid as concerned in producing her bad condition.)

April 2: Has not seemed as bright lately. Mouth is open all the time. Adenoids are felt. Increase thyroid to gr.  $2\frac{1}{2}$  a day.

Jan. 10, 1910: Doing well. Height,  $45\frac{1}{2}$  inches. Weight,  $56\frac{1}{2}$  pounds.

November 21: Not so bright. Is getting thyroid, gr. 3 a day. Increase to gr. 4. Skin is rough and there are some sores on nose. Used unguent-salicylic acid to arms and body.

Nov. 25, 1910: Skin same. (Change of doctors to an enthusiast.)

May 12, 1911: Memory poor. Poor pupil at school. Still has enuresis. Increased thyroid to gr. 6 a day. Weight,  $59\frac{3}{4}$  pounds.

June 7: Went one night without urinating. Adenoids by palpation. Increase thyroid to gr. 9 a day.

June 28: Scab on nose returns. Urinates frequently. Diminish thyroid to gr. 6 a day.

Sept. 18, 1911: Very nervous. Go to thyroid gr.  $4\frac{1}{2}$  a day, with potassium arsenite, gr.  $1/100$  t. i. d.

Jan. 29, 1912: Enuresis pronounced. Backward at school. Bulimia. Thyroid to be gr. 5 b. i. d.

February 14: Reduce schooling. (About this time according to mother, patient received thyroid gr. 15 a day, B. W. & Co.)

September 18: Nervous. Getting thyroid gr. 5 b. i. d.

Feb. 26, 1913: (Enthusiast resigned.) Now aged 11 years. Large and growing well. She wets the bed, however, every night. Very nervous and irritable; has ugly attacks. Nervousness amounts almost to a tremor. Appetite excessive. Often eats all the food on the table (one morning ate eight rolls). Has been thought to have St. Vitus' dance. Dull in school; cannot pay attention. Pulse 120. No murmur. Weight, 73 pounds. Height,  $53\frac{1}{2}$  inches. Stop medicine two weeks.

March 12: Not quite so nervous. Didn't wet last night for first time. Continue. Weight,  $77\frac{1}{2}$  pounds.

March 26: Wet two out of fifteen nights (best in years). Not nervous now.

April 9: Is not nervous and does not wet at all. Appetite is fine. Resumed one-half 5 gr. tablet a day. Weight,  $83\frac{3}{4}$  pounds.

April 23: Wet once, the first day of taking thyroid. There seems to be no difference except skin, which assumed a grayish cast at last visit, but now is clear again. Is much brighter in school and much livelier since the thyroid was stopped first. Before this did not pay attention to remarks, but now is keener than the others. Again omit thyroid. Weight,  $83\frac{3}{4}$  pounds. Height, 54 inches.

May 7: Seems very well indeed. Color is all right; just as good without thyroid as with it. Does not think of enuresis any more. Weight,  $84\frac{1}{4}$  pounds.

May 21: Seems O. K. Never thinks of wetting. Now going a whole day to school, which tires her somewhat. Weight, 87 pounds.

June 4: All right in every way. Now eats rationally.

June 18: Body examined. Arms go down  $7/15$  of distance to knee from anterior superior spine. Shows signs of maturing. Breasts are becoming prominent and there is a little hair on vulva (between labia). Is progressing with her reading and can no longer be fooled by words spelled out. Writes well and with ink, which she could not do formerly because of tremor. Weight,  $89\frac{1}{2}$  pounds.

July 16: All right in every way mentally. Appetite quite easily satisfied. Weight, 91 pounds.

August 11: Fine. Continued without thyroid. Weight, 94 pounds.

September 10: Has been ill for four or five days. Has had no appetite and color has been poor. The color resembles the condition in April when thyroid was resumed with the idea that its absence made color poor. Stools and urine not noted. Gave calomel gr. 2 and rhubarb and soda. Weight, 93 pounds.

September 22: Was all right after calomel. Weight, 96½ pounds.

Jan. 27, 1914: Since last note patient has not been seen so frequently, as she was doing well, growing heavier and apparently holding her own mentally. She has, however, been growing very slow in her motions and inclined to lie abed. She is also hard to waken. Her flesh is hard and rather thick. Her color is good and she has an intelligent expression. With the idea that she must need some thyroid, although she seems to do well without it, she has been given for seventeen days capsules of Dr. Kendall's thyroid "B" which is supposed to stimulate the mentality and lessen thickening of the skin. She wet her bed first night of taking this, but this may have been accidental. Her appetite has been better but she is very slow. She has been more talkative in school. She looks very much heavier than when last seen and her facial expression is different. She looks older, rather sullen and heavy—a leonine expression. She skates well but is slow in getting started. She is a splendid sewer and very ingenious at this. Weight, 106 pounds. Height, 54½ inches. Continue without medication. Have roentgenogram of sella turcica and test sugar tolerance.

February: Roentgenogram shows enlarged sella turcica.<sup>2</sup> A. P., 14 mm.; D., 9 mm. Wrist shows practically normal ossification for age. Pisiform nucleus just beginning to show. Test for sugar tolerance. By mistake, patient took 250 gm. glucose instead of 150 gm. Urine examination normal; no sugar. General condition about the same, a large, notably well-developed (secondary sexual characteristics) girl, of pleasant disposition, very chunky and solid, with a stolid expression and a skin which is thickened and of a yellowish cast, not a cretinoid type. Pituitary?

March 19: Child has been getting more peculiar in appearance. Looks like a little ugly young woman rather than a child; face is heavy and sullen; lips rather thick, nose stubby; neighbors say she looks older. This is accentuated by the development of her bust. Skin is thick, particularly over thighs, abdomen and buttocks. Seems to be due to a deposit of subcutaneous fat, for the skin is somewhat nobby like a stretched lipoma but there are no localized fatty tumors. Hands are broad, with stubby fingers and the skin around the finger nails is scaly. Skin over elbows thick and scaly. Occasionally flushes and has a good color. Is very strong. Appetite good, not excessive. Weight, 106½ pounds. Height, 54½ inches.

Disposition is happy, usually, but has sullen fits and ugly fits. She is fond of reading which she has learned to do since February, 1913. She seems to understand what she reads.

Sleeps well; very hard to wake; goes to bed early. Is eager to play but is a little slower than other children. Loves music and seems to be learning this. Dances well—can do all kinds of modern dances and learns these quickly and better than anything else. Is clever with needle and can trim hats. Will not take cold water baths now. (This was thought due to poor circulation of skin, which feels rather cold and unpleasant to the touch.) (Fig. 1.)

2. Potts: Jour. Am. Med. Assn., Sept. 27, 1913, p. 1188. Average of forty-one normal adult sellae: A. P. 10.8; D. 7.7; maximum 16; D. 10. Children, 12 years, A. P. 7, D. 10; 6 years, A. P. 8, D. 6; 4 years, A. P. 7.5, D. 7; 15 years, A. P. 10.5, D. 7.

Is to have capsules of pars intermedia of pituitary prepared by Mr. Perry.<sup>3</sup>

April 6: Has been taking pituitary capsules for two weeks. Weight, 106 pounds. Height, 54½ inches. Expression is a little brighter. Said "hello" briskly when she came into office. Mouth shuts a little better. More noticeable is the increased smoothness of the skin and "thinning" over the lower thorax. Still doesn't wake up unless shaken. A slow dresser. Continue.

April 22: Face has lost vacant, indifferent leonine look. Expression brighter. Still awfully sleepy in morning. Lazy; does not want to walk. (Due to weight?) Appetite O. K. Bowels more or less constipated. Skin has improved. Skates well when she gets started. Seems worse than ever about coming when called. Weight, 108 pounds. Urine not so abundant. Attempt to test sugar tolerance difficult because of tendency to vomit; 150 gm. glucose not followed by any glucosuria. (May weight be due to several attempts with glucose?)

May 25: Had indigestion at time of trying tolerance. Vomited glucose five times. Has been taking capsules for two months. Out of them last few days. Expression shows improvement. Skin shows improvement. Is just as



Fig. 1 (Series 1).—Author's patient, taken March, 1914.

heavy a sleeper. Begins to take her own part against others and "scraps." In play has not initiated anything; still slow. School work still not good, and she talks a good deal and gets poor deportment marks. Breasts continue to enlarge and the hair on vulva to become longer and thicker. No menstruation. Appetite is not so good; just over indigestion; bowels more or less consti-

**3. Preparation of Pars Intermedia Capsules.**—The material is collected at the abattoir on the morning of killing. The fresh pituitary gland of the bullock is taken to the laboratory within fifteen to thirty minutes of the killing. The pars intermedia is dissected off and dried at once, the drying being completed within forty-five minutes. It is mixed with milk-sugar and the finished product in capsules may be ready within one and a half hours after killing. The pars posterior is not included. Each capsule represents as nearly as possible, the pars intermedia of 150 pounds of live bullock. These capsules will keep in the cold for a year. The great essential is promptness in drying after removal of gland, as bacterial action may destroy the active principles in a very short time. Any preparation made from glands kept in cold storage or as much as twenty-four hours old will probably be much less efficient if not inert. Dr. Kendall's preparation could not be continued because he ran out of his first lot, and a second supply made from another lot of thyroid—somewhat old—was inert.

pated; gets medicine every Friday night. Blood examination (figures lost) showed nothing abnormal in differential. Specimen of urine one week after stopping capsules showed no glucosuria after 150 gm. glucose. She stands up straighter and has grown  $\frac{5}{8}$  inch. Weight, 105 pounds. Height, 55 $\frac{1}{4}$  inches.

Two observers independently have noticed a change in her hands, which is apparent today. Hand has a less heavy, blunt look. Fingers are more tapering. Hand is distinctly more pleasing to the eye and skin is softer. Nothing detected about feet. There is a change in the lower extremities; legs are more approximated; not so great a deviation; ankles can be more nearly brought together. Complexion not so yellow, in fact almost pink and white. Disposition pleasanter; not sulky; takes and gives jokes. Resume capsules.

July 6: Tanned. Appetite good but not too good. More or less constipation. Sleeps well; waked a little more easily. Plays actively; cannot yet keep up with other children, but does not mind. Initiates games and roller skates faster. Laughs easily and is very quick at repartee, which is a great change. Not much change in school work. (Goes to a parochial school where the pedagogic method may not be adapted to her.) Skin is nice and soft. Hips are more slender. Hands better shape. Hair more oily. Breasts larger. Hair on pubes. Legs are hard as iron. Abdomen still pendulous and lordosis noticeable. Bicuspid said to be abnormal. Teeth are generally good.

October 2: Has not had any pituitary for two weeks. Took it all summer during my absence, working it up to four capsules a day once when she had a month of rather bad temper. Is talkative and inattentive in school. Has been promoted but finds all day hard. Skin is still good, but face is a little heavy. Wakes much more easily. Breasts well developed. Hair has increased. Blood pressure, systolic, 90; diastolic, 50; pulse rate, 84. Weight, 106 $\frac{1}{4}$  pounds. To try what effect, if any, adrenal has. Tabloid adrenal gr. 5 O. D.

October 23: Skin yellow, pimply. Not so well. Stop adrenal. Give thyroid B. W. Co. gr. 3 a day. Sphygmomanometer out of order.

November 7: Been on thyroid gr. 3 a day. Height, 55 $\frac{1}{2}$  inches. Weight, 103 pounds. Is brighter and quicker. Skin is drier than when taking pituitary. Look is keener and more thoughtful; not so indifferent and smily. Hands are less tapering than they were last June.

November 14: Look is more straightforward. Gets up of her own accord. Sews a lot and has considerable initiative. Likes to read a lot and to be alone. Very talkative since taking thyroid. Arithmetic her *bête noir*. To have gr. 1 thyroid b. i. d., and one pituitary capsule.

November 28: First five nights on which she took two medicines she wet four times (first in about a year). Mother thinks she has improved. Gets up better. Not brighter in school. Still talkative. Wants to go out more. Pulse, 100. Weight, 103 pounds. Height, 55 inches. Skin again soft and smooth. Continue.

December 12: Better than she has ever been. Brighter. Color better. Expression is best yet; intelligent and thoughtful. Plays actively; is not now always the last one. But is inattentive in school. No wetting. Weight, 102 $\frac{3}{4}$  pounds. Skin has improved; even on belly it is softer, smoother and thinner. Hands taper. Hair on pubes same. General figure is slenderer.

December 18: Has wet five out of six nights. Not so good tempered and possibly not so bright. Color not so good this week. Pulse, 84. Blood pressure, 90-50. Weight, 101 $\frac{1}{2}$  pounds. Stop thyroid one week. Continue pituitary. Glucose, 100 gm.; had tolerance for this.

December 29: Tomorrow aged 13 years. Has had a cold. Color was not quite so good a week ago; better now. Does not seem quite so fine as when she got thyroid gr. 2 and one capsule, but weight is better and has not wet bed.

Has become very inquisitive in the last couple of weeks and notices things she would never notice before. Appreciates things better. Initiative still



increases. Does not want to be alone so much. Plays well. Is more self-conscious than formerly. Begins to care what she has to wear. Has more individuality, which is shown also in expression of face; is more thoughtful and more aware of being an individual. She has always been sympathetic. Her movements are very decently active and alert. She dresses herself quite expertly and is precipitate in undressing. Is very strong physically. No menstruation. To have gr.  $\frac{1}{2}$  B. W. thyroid a day. One capsule pituitary. Weight, 102½ pounds. Height, 55½ inches.

Jan. 14, 1915: For the first few days on gr.  $\frac{1}{2}$  thyroid was ugly and general color was not so good. Mental condition about the same; is a little slow in getting ready for school. Appetite good; eats plenty. Fingers are quite normal. Hand is noticeably of nice contour. For the first time ankles can go into an ordinary shoe without changing buttons. Weight, 104¾ pounds. Height, 55½ inches.

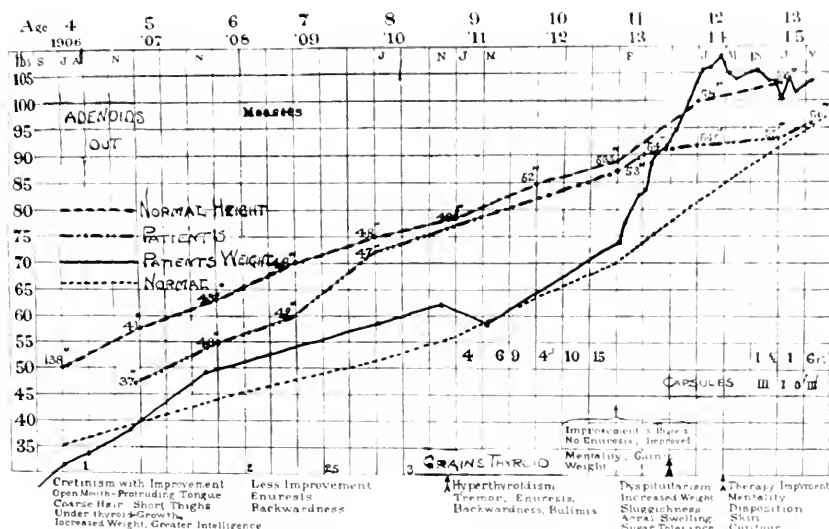


Fig. 2.—Chart showing patient's progress in weight and height with thyroid, with excessive thyroid, without thyroid, with pituitary alone, and with pituitary and thyroid. Also indications as to change in mental characteristics.

January 29: Does not look so well as last time. Nails are again scaly. Weight, 103½ pounds. Give gr. 1 thyroid a day and one capsule pars intermedia. Photograph by Dr. Kilmer (Series 2).

February 24: There is a noticeable change in figure toward slenderness and normal contour. Said to have "a shapely figure." Skin is very soft and smooth except a little at finger tips. Face has a good expression of quiet intelligence. Pubic hair is quite abundant. Breasts large. Lordosis not so noticeable. No wetting. Bowels constipated (to have cascara).

Mathematics still a stumbling block; is much better at dressing; gets up more willingly; plays well and keeps up with the others at play. Still inattentive at school. Nice whistler and dancer. Very fond of reading such books as "Five Little Peppers" and the Alger books. Very full of questions. Clever enough to be always away at dish-washing time. Shows some imagination. Said, "I wonder what I would have been like if I hadn't been going to him" (Dr. Haynes). Pulse, 80. Head, 22½ inches. Chest, 28½ inches. Trochanters, 34. Weight, 103 pounds. Height, 55½ inches. Here planned to stop pituitary

to see if it really was necessary and had done what it had been thought to do. Not ordered stopped.

March 16: When she came into the office she seemed sick in some way which was determined to be a more sluggish expression and a yellower color and slightly swollen face. Determined not to stop pituitary yet, when mother told me that she had understood me to say stop it and had done so two weeks before. Face distinctly heavier; skin rougher on hands, arms, back, and buttocks. Face pimply. Anterior surface of body about same. Curvature of back more like first picture. Has been sullen and irritable. Continue without pars intermedia capsules.

April 1: Still without pars intermedia. Skin roughened in spots, particularly back of arms, thighs and buttocks. Laugh seems less intelligent; said to talk sillier things. Hair on pubes increased. Breasts larger and patient is aware of them. Apropos of their prominence said, "I know I am going to have children when I grow up." No axillary hair. Hands blunter.

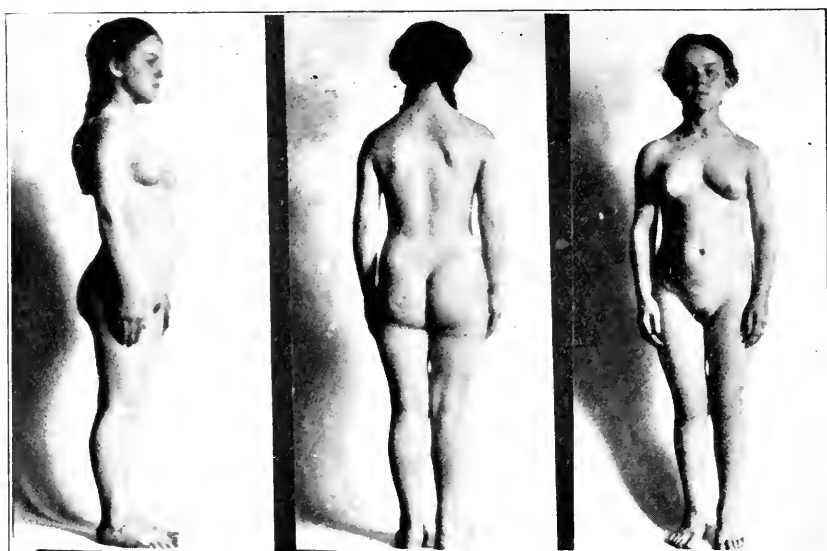


Fig. 3 (Series) 4).—Taken May, 1915. Had been receiving one to three capsules a day, and 1 gr. B. W. Co. thyroid since April 13.

April 12: Still without pituitary. Having thyroid, gr.  $\frac{1}{2}$  b. i. d. Is cross and ugly. Face heavier. Looks heavier in motions and figure is less symmetrical; rather clumsy. (Series 3.) To have 150 gm. glucose. Tolerance. Resume pars intermedia capsules after test.

May 5: Has had two capsules of pars intermedia a day and 1 grain of thyroid.

There is a marked improvement in symmetry since last visit. Skin is finer and noticeably whiter. Skin pretty good around nails; elbows almost smooth again; hands again taper. Breasts larger; more hair on genitals. Hair generally more oily again. Expression more intelligent; happier, gentler, sweeter. Doing better in school. Moves more quickly, both general motions and motions of eyes. A few pimples remain. Try three capsules a day.

May 14: General improvement in color, clearness of face and nails, whiteness and smoothness of skin, which feels warmer and very pleasant to touch. The changes in symmetry are particularly noticeable as before when taking

capsules, in slope of shoulders, slenderness of waist, slenderness of hips, thighs and legs and ankles, and straightness of lower extremities. Less protrusion of abdomen and lordosis less marked. Hands seem lower down than formerly, which may be due to slope of shoulders. Neighbors who have followed case see marked improvement and one not familiar with case would see simply rather a heavy, stocky child, but not an abnormal one. Blood pressure, 100-70; pulse, 72. Weight, 103½ pounds. Height, 56 inches.

May 18: Has tolerance to 150 gm glucose.

May 19: Blood sugar (Dr. O. M. Schloss), 0.058 per cent.; just below normal, 3½ hr. p. c. Binet-Simon test for intelligence, 9 years, with recommendation for special training, with emphasis on teaching from concrete to abstract. (Miss Keller exclaimed on patient's wonderful complexion, its fairness and smoothness.)

Roentgenogram of sella, 15 mm. A. P.; 9 mm. D. (This photograph probably was a distorted view, as it was not taken with especial care to avoid distortion.)

Roentgenogram of wrist normal for age; pisiform showing.

May 22: Administration of two capsules at 12:30 p. m. Administration of 150 gm. glucose at 1 p. m. Injection of 0.5 c.c. Parke Davis "p Pituitrin" into subcutaneous tissue of right arm.

Blood pressure before taking capsules, systolic, 107; diastolic, 75; pulse, 72. After injection, systolic, 105; diastolic, 70; pulse, 72.

Urine first six hours, 1.036; faint trace of sugar; last eighteen hours, 1.030; no or very faintest trace.

Height and weight of other members of her family: Sister, aged 16 years, height 67 inches; weight 132 pounds; father, height 74 inches, weight 214 pounds; sister, aged 19 years, height 67 inches, weight 145 pounds.

# THE SPINAL FLUID IN POLIOMYELITIS AND ITS DIFFERENTIATION FROM FLUIDS OF OTHER INFECTIONS \*

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A review of the literature reveals comparatively few extensive studies of the cerebrospinal fluid in acute poliomyelitis. This fact is due perhaps to the lack of opportunities for such studies, or to the failure to appreciate the value of the changes in such fluids.

Wickman<sup>1</sup> in his exhaustive monograph on poliomyelitis pays only scant attention to the subject of the fluid in this disease. Römer and Joseph,<sup>2</sup> too, slight the value of examination of fluids in their discussion of diagnosis. They have been particularly interested in the attempt to demonstrate specific substances in the fluid and serum by complement fixation. In this attempt they have failed, as also have Wollstein<sup>3</sup> and Gay and Lucas.<sup>4</sup>

Plaüt,<sup>5</sup> Rehm and Schottmüller devote a page to the cerebrospinal fluid of poliomyelitis in their book on cerebrospinal fluids. They say that cerebrospinal fluids in poliomyelitis contain no globulin and that the average cell count is 15 per cubic millimeter.

Forbes<sup>6</sup> reports the examination of 33 cerebrospinal fluids of which 8 were bloody, due no doubt to accident in technic. Of these, 24 contained albumin in varying amounts. Six showed a heavy precipitate. Cytologic examination showed increase of cells in all but 6, twenty-one fluids having only a slight excess. Very few polymorphonuclears were found, small mononuclears being the most common type. He found that the cell reaction was in direct proportion to the albumin content. All of these cerebrospinal fluids reduced Fehling's solution normally.

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1. Wickman, Ivan: *Jour. Nerv. and Ment. Dis.*, Monograph 16, 1913.

2. Römer and Joseph: *München. med. Wehnschr.*, 1910, vii, 568.

3. Wollstein, Martha: *Jour. Exper. Med.*, 1908, p. 476.

4. Gay and Lucas: *Arch. Int. Med.*, 1910, vi, 330.

5. Plaüt, Rehm and Schottmüller: *Leitfaden zur Untersuchung der Zerebrospinal flüssigkeit*, Gustav Fischer, 1913.

6. Forbes, J. G.: *Lancet*, London, Nov. 18, 1911.

Morse<sup>7</sup> reported thirteen examinations of cerebrospinal fluids in seven cases and found pathologic changes in all. All fluids were clear, with one exception, and this was opalescent. The small mononuclear cell was the predominating type of cell. He does not find any aid from the examination of the spinal fluid in differentiating poliomyelitis in preparalytic or abortive form from tuberculous meningitis.

Gay and Lucas<sup>4</sup> have made an interesting cytologic study of spinal fluid from 6 cases of monkey poliomyelitis, noting changes in all stages of the disease. In the incubation period the cells were increased from 100 to 300 per cubic millimeter. They were largely of the large mononuclear type with some polymorphonuclears. In the prodromal period the count went up to 1,000 per cubic millimeter. In this stage polymorphonuclears were increased, in some cases, up to 60 per cent. In the early acute stage, the increase of cells was still very great but the lymphocytes were the predominating cells. At the end of a week or ten days, there were very few cells present, mostly large mononuclears and a few polymorphonuclears. They also report on thirteen spinal fluids from 4 human cases, all of which showed the large mononuclear cell present in varying numbers.

Probably the best and most comprehensive study of the cerebrospinal fluid in poliomyelitis in the American literature is that of Peabody, Draper and Dochez.<sup>8</sup> They tabulate and analyze the findings in 233 spinal fluids from 69 patients. The conditions of their study were such as to permit the following up of the changes in the fluid from week to week, and they have compiled the results admirably. All but two of the cases presented abnormal changes either in cell content or chemical constituents, most frequently in both. The predominating type of cell was the small mononuclear. In some cases, early in the disease, polymorphonuclears were present up to 80 to 90 per cent. of the total count. Mention is made of large phagocytic cells, containing vacuoles and broken down cells as being present in some cases. A grouping of the spinal fluids into two distinct types is made, the one with a high cell count and a low globulin content; the other, with a comparatively low cell count and a high globulin content. The former is found most frequently in the early part, and the latter in the later part of the acute stage.

Four preparalytic and two abortive cases are included in this report and are of particular interest inasmuch as these are the types of cases that present the greatest difficulty in diagnosis. Two of these patients that developed paralyzes showed a high cell count. Three

7. Morse, J. L.: *Arch. Pediat.*, 1911, xxviii, No. 3.

8. Peabody, Draper and Dochez: *Monograph 4, Jour. Exper. Med.*, June 24, 1912.

others showed only a moderate increase in cells. Of these two developed paralyzes and one was an abortive case. The remaining one, an abortive case, presented a normal spinal fluid on first examination, but the cells were found increased in later specimens. They urge that though the cerebrospinal fluid of poliomyelitis does not present a specific picture, it is of the utmost value as an aid, particularly when considered in conjunction with the clinical aspects of the case, in clearing up the diagnosis in the abortive type and in the preparalytic stage.

The material for the present report was taken from the records of the meningitis department of the New York City Board of Health and covers a period of four years. It consists of the examination of forty-seven cerebrospinal fluids from twenty-nine patients, twenty-seven of which were seen by members of the meningitis staff in consultation with physicians throughout the city. Comparatively few of these patients were seen more than once, and we were, therefore, unable to observe the changes in the various stages of the disease that the Rockefeller Institute workers so ably described. However, this work compensated in the great interest produced by the necessity of arriving at a correct diagnosis through the examination of the spinal fluids, as the majority of the cases were of the meningitic and encephalitic varieties.

Of the 47 fluids, 2 were contaminated by blood and 2 were otherwise unreliable. Of the remaining 43, 10 were from cases diagnosed as myelitis, 21 from encephalitic, 6 from myeloencephalitic, and 6 from abortive cases. Of the 10 myelitic cases, 5 fluids were examined in the preparalytic stage and 5 in the postparalytic stage. Of the 21 encephalitic fluids, 17 were from patients without paralysis, many of which properly belong to the meningitic type, and 4 were from cases with involvement of the cranial nerves. The 6 fluids of the myeloencephalitic group were obtained from cases that presented involvement of both the cranial nerve nuclei and anterior horn cells. The abortive cases showed no signs of paralysis. We feel quite secure in the diagnosis of the cases not showing paralysis, by the clinical characters and outcome of the cases, and in fatal cases, by the negative results after inoculation into two guinea-pigs.

Of the 43 fluids examined, 28 were obtained in the first week of the disease; 8 in the second week, 5 in the third week and 2 in the fourth week.

The routine of our examination consists of a description of the amount and gross appearance of the fluid; an estimation of the cell contents, as to whether there is no increase, a moderate increase or a great increase. This was accomplished by centrifuging 10 to 15 c.c.

of the fluid at high speed for one-half hour and examining three or four platinum loopfuls of the sediment spread on a slide and stained; a rough differential count of the types of cells present; also making note of unusual types of cells. The fluid is then examined bacteriologically on smear and in culture. If smear is negative for organisms, 5 to 10 c.c. of the fluid is inoculated into each of two guinea-pigs. The chemical examination consists of the estimation of the albumin and globulin content and the reduction of Fehling's solution. The albumin and globulin content is graded in  $+$  signs, beginning with  $\pm$  and ascending to  $4 +$ , depending on quantity of precipitate. A  $\pm$  is considered as that very faint haze present in normal fluids, and  $4 +$ , the maximum, represents the very heavy precipitate obtained most commonly in purulent fluids. The reduction of Fehling's solution is graded, negative when there is no red precipitate at the end of 15 minutes;  $1 \pm$  when there is a slight precipitate at the end of that time;  $2 +$  when there is moderate precipitate and  $3 +$ , the maximum, when there is an immediate and heavy reduction. This latter reaction is encountered in practically all normal fluids.

The quantity of fluid withdrawn varied from 5 to 100 c.c. We usually withdraw as much as will readily come, minimizing the suddenness of withdrawal as much as possible. Practically all the fluids that are much in excess of normal come out under varying degrees of pressure, though no direct method of measuring same was used. Thirty-eight fluids were clear; one slightly turbid; one opalescent; three yellowish in color but clear. One of the latter exhibited spontaneous coagulation, the so-called syndrome of Froin.<sup>9</sup>

#### CYTOLOGY

Of the 43 fluids, 15 showed a great increase; 24 a moderate increase and 4 no increase in cell content. Of the latter, one was from a paralytic case, fifteenth day of disease, with a  $4 +$  albumin and a  $3 +$  globulin reaction; another from a paralytic case, sixth day of disease, with no increase in albumin or globulin; one from an encephalitic or meningitic case, third day of disease, with a  $1 +$  albumin and globulin reaction.

The small mononuclear cell or lymphocyte predominate in all but five fluids, viz., 88 per cent., in proportions varying from 60 to 100 per cent. These five show 95 per cent., 85 per cent., 75 per cent., 70 per cent. and 60 per cent. polynuclears, respectively. Of these, three were withdrawn on the third, fourth and fifth day of the disease. Of the two remaining, the date of withdrawal is unknown. Eight other

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9. Froin and Foy: *Gaz. d. h p.*, November, 1908.

fluids in which the small mononuclear predominates show a polynuclear content of from 15 to 40 per cent.

A cell that has been increasingly attracting our attention is the large mononuclear or perhaps endothelial cell. Many of them contain larger and smaller deep staining granules in their rather generous proportion of cytoplasm. This type is a rather rare find in fluids of tuberculous meningitis, in which fluids the cells are practically all of the very small mononuclear variety, with a hardly discernible rim of cytoplasm around the nucleus. We have also seen cells with polyform nuclei, described by Flexner and Lewis<sup>10</sup> as being present in a fluid of experimental poliomyelitis in the incubation and prodromal periods. When we find the large mononuclears in appreciable numbers in a smear from a clear fluid, we think of poliomyelitis. While we do not consider this type of cell pathognomonic of poliomyelitis, yet their presence warrants a strong suspicion of poliomyelitis.

As 65 per cent. of our fluids are from patients in the first week of the disease, we were unable to trace any relationship between cell content and stage of disease. There was no increase in cells in 3 fluids of the first week and in one of the second week; a moderate increase in 14 of the first week; 3 of the second week; in 1 of the third week. There was a great increase in 7 of first week; in 3 of second week; 2 of third week and in 1 of fourth week.

#### BACTERIOLOGY AND ANIMAL INOCULATION

Examination of smear for organisms, particularly the tubercle bacillus, has been uniformly negative. Cultures have been sterile except for an occasional evident contamination. Animals inoculated with 5 to 10 c.c. of the fluid have, after 4 weeks, borne the injection of 1 c.c. of concentrated crude tuberculin without lethal effect.

#### CHEMISTRY

All but three fluids showed increase in the albumin and globulin content. These three were from cases in the first week of the disease.

Our findings, on the whole, show a higher albumin and globulin content in the encephalitic cases than in those of the myelitic type. This is true particularly of the nonparalytic encephalitic variety, in which the meninges are no doubt more actively involved in the inflammatory process. Of the 17 fluids in this nonparalytic encephalitic group, four show 4+ albumin and globulin; one 3+, seven 2+, four 1+ and one negative albumin and globulin. Of the 4 paralytic encephalitic fluids three showed 1+ albumin and globulin and one 3+ albumin and globulin. Of 16 myelitic fluids only one exhibited a 4+

10. Flexner and Lewis: Jour. Am. Med. Assn., 1910, liv, 1140.



albumin and globulin. This was a heavy yellow fluid that coagulated spontaneously. Of the remaining 15, two had 2+ albumin-globulin; twelve 1+ and one negative albumin-globulin. The six fluids from abortive myelitic cases all showed a 1+ albumin-globulin content. The findings of increased albumin and globulin content in the encephalitic type of fluid approach those encountered in tuberculous fluids, though 4+ albumin and globulin are comparatively fewer in the latter type of fluid. This tends to increase the difficulty of differential diagnosis.

TABLE 1.—ALBUMIN-GLOBULIN CONTENT OF CEREBROSPINAL FLUID IN DIFFERENT TYPES OF POLIOMYELITIS

Type	Albumin-Globulin					Total
	—	+	++	+++	++++	
Non paralytic encephalitic..	1	4	7	1	4	17
Paralytic encephalitic..	0	3	0	1	0	4
Myelitic .....	1	12	2	0	1	16
Abortive.....	0	6	0	0	0	6

TABLE 2.—RELATION OF ALBUMIN-GLOBULIN TO DURATION OF DISEASE

Duration Disease	Relation of Albumin-Globulin to Duration of Disease					Total
	—	+	++	+++	++++	
First week...	2	18	7	1	2	30
Second week..	1	3	2	1	1	8
Third week...	0	2	2	1	0	5
Fourth week..	0	1	0	0	1	2

We could find no definite relationship between the albumin-globulin content and duration of the disease. However, our findings do show that of 21 fluids that gave a 1+ albumin-globulin, 80 per cent. were from cases under 8 days' duration, whereas of 18 fluids that gave 2+ or better, only 40 per cent. were from cases under 8 days' duration; while 3 fluids that had no increase in these contents were respectively of 3, 6 and 9 days' duration. From these figures one might infer, not too definitely to be sure, that albumin and globulin are on the increase in the later stages of the acute disease. This is in harmony with the findings of the Rockefeller Institute workers. They also find that there is a gradual diminution in the globulin content in the more chronic stage of the disease.

## RELATION OF CELL CONTENT TO ALBUMIN-GLOBULIN CONTENT

Of the four fluids showing no increase in cells, one, a yellow fluid, shows a 4 +, one a 1 + and 2 no albumin-globulin. Of 22 fluids showing a moderate increase in cells, one shows a 4 +, one a 3 +, five 2 + and fifteen 1 + albumin-globulin. Of seventeen with a great increase in cells three show 4 +, three 3 +, three 2 + and eight 1 + albumin-globulin. From these findings one could infer that the cell content parallels that of albumin and globulin. These figures agree with those of Forbes but differ from those of the Rockefeller Institute workers, who found two types of fluid, the one with high cell and low globulin in the early part of the acute stage, and the other a low cell and a high globulin in the later part of the acute stage. Our report deals largely with fluids from encephalitic or meningitic cases, which may account for the discrepancy.

Interesting to note is the fact that all three of our yellow fluids gave a 4 + albumin-globulin test, and that two of them that were tested with reduction of Fehling's solution gave only a very slight reduction.

TABLE 3.—RELATION OF CELL CONTENT TO ALBUMIN-GLOBULIN

Cell Increase	Relation of Cell Content to Albumin-Globulin					Total
	—	+	++	+++	++++	
None .....	2	1	0	0	1	4
Moderate ....	0	15	5	1	1	22
Great .....	0	8	3	3	3	17

## REDUCTION OF FEHLING'S SOLUTION

Only fifteen of our fluids were subjected to the test of reducing Fehling's solution. All of them reduced, but not in equal degree. Twelve gave a 3 + or maximum reduction and three a 1 + or minimum reduction. The relationship existing between the reduction of Fehling's and the albumin-globulin content is quite definite. The three fluids which show a 1 + Fehling's, show a 4 + albumin globulin, whereas of the 12 that show a 3 + Fehling's, none exceed 2 + and most of them show a 1 + albumin-globulin test. This relationship, in our experience, is common to all pathologic fluids. The presence of the reducing substance in varying degree, or its total absence, is the most important of chemical reactions of spinal fluids from the view point of prognosis. Thus we are able to say of a case of meningococcic meningitis before the fluid is free of organisms, that the inflammatory process is receding, by noting the return of the reducing substance.

Vice versa, we regard unfavorably a purulent fluid that clears up without the return of the reducing substance. In tuberculous fluids, its presence or absence indicates the extent and severity of the inflammatory process. A fluid that fails to reduce indicates an extensive and severe pathologic change.

#### DIFFERENTIATION OF CLEAR FLUIDS

The clear fluids besides those of poliomyelitis that we meet with in our work are obtained from cases of meningism accompanying pneumonia, the acute infectious diseases, and some cases of gastro-enteritis; from cases of tuberculous meningitis and from an occasional case of epidemic meningitis in which the patient is recovering. We have met with one opalescent fluid from an atypical case of rabies that strongly resembled polioencephalitis. This fluid presented a high polynuclear count and no organisms in smear and culture, comparatively low albumin-globulin and good reduction of Fehling's solution. We called it polioencephalitis until animal inoculation of the brain material proved it to be rabies.

We experience no difficulty in determining a fluid from a case of meningism, as it uniformly, in our experience, shows no increase in cells, no albumin-globulin, and a prompt and heavy reduction of Fehling's solution. Lucas<sup>11</sup> includes this type of fluid as presenting a cell picture similar to that found in encephalitis, poliomyelitis and tuberculous meningitis. With this we do not agree, as in none of our meningism fluids have we found an increase in cells.

The spinal fluids of patients recovering from epidemic meningitis present considerable difficulty in differentiation. They are, however, distinctly more turbid than the poliomyelitis fluids; there is a persistence of a high polynuclear content; high albumin-globulin test. These findings in conjunction with the clinical features of the case tend to clear the diagnosis.

The fluid that presents the greatest difficulty, and this is many times insurmountable, is that of tuberculous meningitis in which the tubercle bacillus has not been found. Of our last 43 tuberculous fluids the organism was found 23 times, or 53 per cent. All but one of these fluids were clear. All had a preponderance of the small mononuclear cell, 85 per cent. to 100 per cent. of the total count. Comparatively few presented the large mononuclear cell, and when present, only in small numbers. Five had 1 +, eighteen 2 +, sixteen 3 + and four 4 + albumin-globulin. The behavior towards Fehling's solution is quite different from that of poliomyelitis fluids. Twelve produced no reduction; 21 only a very slight reduction, 6 a 2 + and 4 a 3 + reduction.

11. Lucas: *AM. JOUR. DIS. CHILD.*, 1911, i, 230.

TABLE 4.—SHOWING ALBUMIN-GLOBULIN CONTENT AND REDUCTION OF FEHLING'S SOLUTION

	Albumin-Globulin						Reduction of Fehling's Sol.				
	—	+	++	+++	++++	Total	—	+	++	+++	Total
Poliomyelitis, . . . . .	2	25	9	2	5	43	0	3	0	12	15
Tb, Meningitis, . . . . .	0	5	18	16	4	43	12	21	6	4	43

It is to be noted also that the albumin-globulin content is higher in the great majority of tuberculous fluids. Approaching these in this respect are the fluids of the encephalitic group. Hence, a clear fluid, free from tubercle bacillus, with a high small mononuclear count, comparatively high albumin-globulin content and low in reducing substance, is more apt to be tuberculous than poliomyelitic.

A very important point in determining the diagnosis of a case with the fluid findings described as being present in either poliomyelitis or tuberculous meningitis is to be had in the history of the case. If there is an acute onset with high fever, 103 to 104, in a previously healthy person, we do not hesitate to make a tentative diagnosis of poliomyelitis. Sudden onset in tuberculous meningitis is an exceedingly rare occurrence. An excellent table of differential points in the examination of spinal fluids has been furnished by Du Bois and Neal.<sup>12</sup>

As to the value of lumbar puncture and examination of the spinal fluid, too much cannot be said in its favor. It can be made the means of clearing up the diagnosis in puzzling cases presenting meningeal or cerebral symptoms. Peabody, Draper and Dochez,<sup>8</sup> Lucas<sup>11</sup> and Frissel,<sup>13</sup> present evidence of definite aid in 18 cases of poliomyelitis in the preparalytic stage. The technic of lumbar puncture is simple and safe and the examination of the fluid is not complex.

#### CONCLUSIONS

1. The cerebrospinal fluids of poliomyelitis and encephalitis show abnormal changes in practically all our cases.
2. The fluids of poliomyelitis and encephalitis present no specific characteristics.
3. Fluids from cases of encephalitis generally show a higher albumin-globulin content than do the fluids of myelitis or of the abortive cases.
4. Fehling's solution is reduced by all fluids but not in equal degree.
5. Examination of the spinal fluid is the most important factor in clearing up the diagnosis in abortive and preparalytic cases.

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12. Du Bois and Neal: Summary of Four Years of Clinical and Bacteriologic Experience with Meningitis in New York City, *AM. JOUR. DIS. CHILD.*, January, 1915, ix, 1.

13. Frissel, L. F.: *Jour. Am. Med. Assn.*, 1911, lvi, 661.

A CLINICAL STUDY OF TWO HUNDRED AND TWENTY-  
EIGHT CHILDREN IN RELATION TO TUBERCULOUS  
EXPOSURE CONTROLLED BY VON PIRQUET  
REACTION \*

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AND

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This paper represents a clinical study of 228 children coming under our observation during the past two years as volunteer workers in the Saturday morning children's clinic of the tuberculosis division of the Seattle Department of Health. It should be understood at the outset of this paper that these children represent a group in the community most likely to give evidence of tuberculous infection, since the large majority are children from tuberculous homes. Many other children were seen who cannot be included in this series owing to the incompleteness of their records. The reasons for this are unavoidable, since many children come to the clinic but once, and no opportunity is given either for the observation of the von Pirquet test or to confirm any conclusion reached at the time of the first visit. For purposes of convenience in the filing and handling of records in the clinic some definite classification of these cases must be made. Every one coming in contact with tuberculosis in childhood and infancy realizes the difficulty, in many instances, which is attached to making a diagnosis. Unless the classification is very general and permits of considerable elasticity, it is likely only to be a source of confusion, since the interpretation of a case often depends to a large extent on the individual inclination of the examiner. Finer degrees and shades of impaired resonance, finer degrees of prolonged expiration, finer shades of harsh breathing and of paravertebral dulness, we all realize are rather uncertain findings on which to form an exact basis of classification.

CLASSIFICATION IN USE IN THE CLINIC

We have divided our cases in the clinic into three general groups, (1) tuberculous, (2) clinically non-tuberculous, (3) non-tuberculous. The tuberculous children represent those children giving clinical evidence of tuberculosis with or without a positive von Pirquet. Clin-

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ically non-tuberculous, those children giving no clinical signs but giving a positive von Pirquet. Non-tuberculous being those children giving no clinical signs and a negative von Pirquet.

There is a large number of cases constantly carried along in the files with diagnosis deferred. These records form that group previously referred to as being unusable in this series. While the above classification is the one in use in the clinic at present, for the purpose of this paper, which is a study in relation to home exposure, these cases have been tabulated somewhat differently: 1. Children with a definite history of exposure. 2. Children with no history of known exposure.

We assume that in a large series of cases such as this, for all practical purposes the cutaneous tuberculin reaction of von Pirquet is nearly as reliable as the *stichreaction*. Veeder, in a recent study of 1,321 children in St. Louis, reached the conclusion that the intradermic tuberculin reaction gave but a slight increase in the percentage of positive cutaneous reactions. The von Pirquet test is made by the nurse, but under our supervision, with one-half strength "old tuberculin." Since these reactions have been carefully made, when they were negative in many instances they have not been repeated. It is difficult in a clinic of this sort to retest each negative reactor, no matter how desirable it might be to do so. Several negative reactions have been repeated once and in some instances twice without change. I feel sure that subsequent cutaneous tuberculin tests made within a short time on those giving a negative reaction at first examination, would have altered our series only to a limited extent. There are 166 children out of the 228 who have been or still are living in intimate contact with active adult cases. In the remaining sixty-two there is no known exposure. These adult contacts, in most instances, one or the other parent, in a few instances both parents, or older brothers or sisters, are in the stage of lung invasion in varying degrees of activity. As many as can be have been segregated at the new City Tuberculosis Hospital at Firland.

#### CHILDREN WITH A DEFINITE HISTORY OF EXPOSURE

There are eighty-four of the 166 children with a definite history of exposure who give a positive von Pirquet test, or about 50.6 per cent. Of this number, as naturally would be expected, the largest part, sixty-nine, or 82.1 per cent., shows no clinical evidence of tuberculosis. It has for some time been the teaching that tuberculosis in an infant progresses rapidly toward a fatal termination. More recently, however, Halm, Ibrahim and Eichelburg have reported cases to prove that prognosis is not absolutely bad in infants. While these children of the clinically non-tuberculous group bear their infection with the tubercle

bacilli without apparent harm, their systems probably being proof against the organism, nevertheless, we attempt a close observation of these children. Each few weeks they return. We have been unfortunate enough in a few cases to observe an inactive tuberculosis assume alarming evidences of activity, even among older children. There are a few from this group, nine in all, in whom one of us has recorded questions of finer shades of impaired resonance or harsh breathing, where one did not at the same time seem justified in regarding such indefinite findings as constitutional signs. It would probably be better to classify these clinically non-tuberculous children as suspicious. There are fifteen children, representing 17.8 per cent. of those children exposed to tuberculosis, who give a positive reaction and clinical evidence of tuberculosis. They show varying degrees of activity and types of infection, including seven cases of bronchial gland tuberculosis, one active keratitis, two with cervical adenitis, four with distinct lung invasion, and one with tuberculous peritonitis. Since this paper was undertaken, one inactive, clinically non-tuberculous child developed an active tuberculous peritonitis right under our personal observation.

Most of those diagnosed as bronchial gland tuberculosis are children with a distinct history of not doing well, with subnormal or slightly elevated temperature, frequently complaining of pain in chest or back, poor appetite, weakness or listlessness, with dilated chest veins, but no physical evidence of tuberculosis except sometimes paravertebral dulness. Radiographs showed corresponding shadows about the right hilus. The absence of any bone cases is due to the fact that we have in Seattle a splendid orthopedic hospital, the Children's Orthopedic Hospital, and cases of that character are early recognized and sent to that institution.

There were eighty-two children with a definite history of exposure who gave a negative von Pirquet. This represents about 49.3 per cent. who give negative reactions out of the total 166 exposed to tuberculosis. One of these children gives distinct clinical evidence of tuberculosis, in which instance, as would be expected, the process has advanced to the third stage. There are eight in whom one of us recorded questions of finer shades of harsh breathing. In view of the fact that cutaneous reaction is negative in the presence of measles, it is only fair to state here that none of these children had measles at this time or within recent date.

#### CHILDREN WITH NO HISTORY OF EXPOSURE

The children we have just been considering were children sought out and brought to the clinic especially, by the nurses of the department, owing to their known intimate contact. These sixty-two children whom we now consider, were brought to the clinic because of



poor nutrition, or by fear that something of the nature of tuberculosis might be present, rather than because of any known exposure. Fourteen of these sixty-two children, or about 22.5 per cent., give a positive von Pirquet, the remaining forty-eight, or 77.4 per cent., give a negative test.

TABLE 1.—REACTIONS OF EXPOSED AND NON-EXPOSED CHILDREN

	Positive von Pirquet		Negative von Pirquet	
	No.	Per Cent.	No.	Per Cent.
166 children exposed .....	84	50.6	82	49.3
62 children with no known exposure .....	14	22.8	48	77.4
—				
228 children .....	98	42.9	130	57.1

It is interesting to note in Table 1 that in the entire series of 228 children, with so large a number having known exposure, the percentage of positive reactions was only 42.9 per cent.

The assertion made by Fishberg<sup>1</sup> that the difference between those who lived in a tuberculous *milieu* and those who had no contact with consumptives in their homes, is apparently insignificant, cannot be borne out by this series. In fact, decidedly the contrary is the case. One encounters many interesting problems in such a series as this, where children exposed to a tuberculous mother and father who are in active stages of lung invasion, should react negatively with every opportunity of infection. Again, one child with equal exposure yields a negative reaction, while all the other children in the family react positively.

In considering the entire series by ages, as a majority of similar investigators have done, we have the results shown in Table 2.

TABLE 2.—RESULTS IN THE SERIES BY AGES

Age	Number Tested	Per Cent. of Positive Reactors	
Under 1 year .....	7	2	28.5
Under 2 years .....	10	7	70.0
Under 3 years .....	12	4	33.3
Under 4 years .....	33	15	45.4
5 to 7 years .....	37	13	35.1
7 to 10 years .....	58	17	29.3
10 to 15 years .....	70	40	58.1

The high percentage of positive reactions under two years is due to the fact that the whole number (10) is not large and nearly all of these were brought in because of a death recently of one or the other parent. Otherwise, the series corresponds in general with similar studies illustrating the fact that the reaction gradually becomes more frequently positive until 10 to 15 years of age, where the maximum is reached.

1. Fishberg: On the Cutaneous Tuberculin Test in Children of Non-Tuberculous Parentage, Arch. Pediat., 1915, xxxii, 20.

## REVIEW OF SIMILAR STUDIES

For purposes of convenience in contrasting these similar studies we have followed the grouping of our cases in a general way with von Pirquet's proposal for an international statistical study of the frequency of tuberculous infection in children. There are many extensive articles on different phases of the cutaneous tuberculin reaction in children, in which this aspect has been neglected or only slightly touched on, which are not usable.

Tabulating for purpose of convenience these similar studies, we have the results shown in Table 3.

TABLE 3.—STUDIES OF TUBERCULOUS REACTION IN CHILDREN

Name	No. of Children Tested	Age at which Largest Percentage of Positive Reactions Are Obtained, Years	Percentage of Reactions
Von Pirquet <sup>2</sup> .....	1,407	13-14	93.0
Hamburger <sup>3</sup> .....	532	13-15	95.0
Hellesen <sup>4</sup> .....	480	10-14	46.0
Shaw and Laird <sup>5</sup> .....	330	over 6	45.0
Meroz and Khalatoff <sup>6</sup> .....	337	10-15	78.6
McNeil <sup>7</sup> .....	541	4- 5	45.0
Sachs <sup>8</sup> .....	217	10-15	60.0
Berberich <sup>9</sup> .....	800	10-15	58.8
Lapage <sup>10</sup> .....	1,000	5-16	60.8
Arieti <sup>11</sup> .....	38	7-11	59.0
Fishberg <sup>12</sup> .....	692	14	83.79
Fishberg <sup>1</sup> .....	588	14	75.0
Veeder and Johnson <sup>13</sup> .. .	1,321	10-14	44.0
Manning and Knott .....	228	10-15	58.1

Fishberg's two series and our own were studied particularly in relation to tuberculous exposure.

COMMENTS ON INFLUENCE OF COMMUNITY CHARACTERISTICS OF  
CLIMATE, HOUSING, SANITATION, ETC.

The disparity of results obtained by various observers cannot be easily explained. T. Frazer<sup>14</sup> is of the opinion that discrepancies must be attributed to differences of technic and to an agreement as to

2. Von Pirquet: Jour. Am. Med. Assn., 1909, lii, 675.
3. Hamburger: Med. Klin., March 30, 1913.
4. Hellesen: Jahrb. f. Kinderh., June 12, 1909.
5. Shaw and Laird: Arch. Pediat., 1909, xxvi, 488.
6. Meroz and Khalatoff: Rev. méd. de la Suisse romande, 1914, xx; abstr. Arch. de méd. des enf., 1913, xvi, 307.
7. McNeil: Edinburgh Med. Jour., 1912, viii, iv, 324.
8. Sachs: Trans. Internat. Cong. Tuberc., 1908, ii, 484.
9. Berberich: Abstr. Arch. de méd. des enf., 1913, xvi, 307.
10. Lapage: Brit. Jour. Child. Dis., 1912, ix, 497.
11. Arieti: La Pediatria, 1913, iii.
12. Fishberg: Arch. Pediat., 1914, xxxi, 96.
13. Veeder and Johnson: AM JOUR. DIS. CHILD., 1915, ix, 478.
14. Frazer, T.: Med. Rec., New York, 1915, lxxxvii, 2, 57.

what constitutes a reaction; as different methods of scarifying, the depth of abrasion, the concentration of tuberculin. The technic is so simple that this factor, we believe, differs very slightly in any carefully observed series. The assertion has frequently been made that nearly all children at 15 years of age are tuberculous. In support of such an assertion the figures already incorporated into this paper, of Hamburger and von Pirquet especially, are quoted. What right have we, however, to assert that what is true of Vienna is true of our own community? One of us (M.) has seen both of these clinics and spent a month in Hamburger's, and has never seen in any clinic so many children with third stage tuberculosis as in Hamburger's clinic. Rather than differences in technic must we believe of far more importance in explaining difference of frequency of tuberculosis in children in different communities, are peculiarities of climate, sanitation and housing of these different communities. Children frequenting the Poliklinik and the Kinderklinik in Vienna come from poorly heated, poorly ventilated, stone houses standing side by side, row after row of five story buildings. Many of these buildings and rooms standing years, probably have been inhabited by more than one generation of consumptives. This situation contrasted with the community characteristics of a new community like our city, must explain these discrepancies. In a climate favorable to open air living, with a community made up of separate houses, and furthermore, with each home a comparatively new, modern house, and probably few, if any, over twenty-five years of age, the number of community foci of tuberculous infection must be far less in Seattle than in Vienna.

#### CONCLUSION

In a clinical study of 228 children in relation to tuberculous exposure controlled by the cutaneous von Pirquet test, we find that, contrary to the findings of Fishberg, children living in tuberculous *milieu* and those with no known contact with consumptives show marked differences; those living in tuberculous surroundings reacting in ratio of about 2 to 1 of those living in an environment not known to be tuberculous. Further, we find the number of positive reactors in the entire series is only 42.9 per cent. We also find that the number of children between 10 and 15 years reacting positively to the cutaneous tuberculin reaction, in a series in which the majority of the children are from tuberculous homes, is 58.1 per cent., far below the figures of Hamburger, 95 per cent., and von Pirquet, 93 per cent.

These discrepancies are due, in our opinion, to community characteristics of climate, housing and sanitation.

# A CONGENITAL MALFORMATION OF THE INTESTINE

## MULTIPLE POINTS OF COMPLETE OBSTRUCTION

L. M. DRENNAN, M.D., AND H. C. CLARK, M.D.

ANCON, CANAL ZONE

According to various authors, congenital malformation of the intestine is not very frequent, aside from imperforate anus. When the rectal malformations are left out of consideration it is stated that the large bowel is much less commonly the site of congenital variations than the small bowel.

Leichtenstern<sup>1</sup> found the proportion of cases in the different situations as follows: 375 at the anorectal junction, 75 in the small intestine, and 10 in the colon.

Holt<sup>2</sup> says that stenosis or atresia may occur at one or more points in the small bowel, but that obstruction is much more frequent in the upper portion, the common seat being the duodenum. Atresia is more often seen than stenosis, the causes suggested for their formation being fetal peritonitis and volvulus.

A review of the literature indicates that but one point of actual obstruction is usually found, while beyond this are sometimes found one or more points of stenosis. The clinical picture produced by such a malformation is that of intestinal obstruction and, as a rule, even surgical intervention can offer little hope of a cure. The duration of life depends on the location of the obstruction. The nearer the stomach the lesion is, the shorter the duration of life.

In view of the infrequency of this condition, and because of the very limited number of cases, if any, of complete multiple congenital obstructions of the jejunal type, we offer this brief case report taken from the surgical service of Dr. A. B. Herrick.

### CASE REPORT

Hospital No. 169112, Baby S., white, male, aged 4 days, local residence, Paraiso, Canal Zone.

*Family History.*—Mother and father in good health; no accident to mother during gestation, so far as could be determined. First childbirth normal and the child continues in good health up to the present. No family history of such an accident in either the maternal or paternal records.

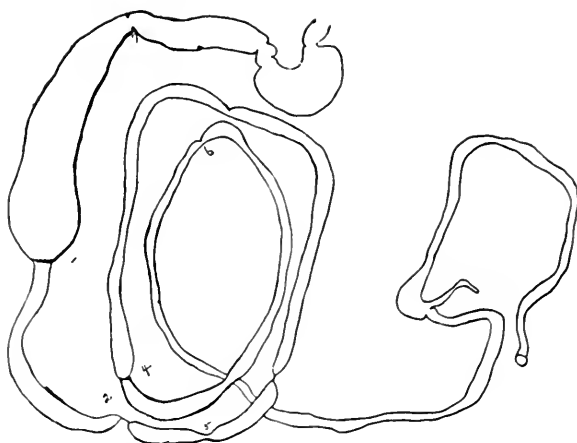
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1. Leichtenstern: *Osler's Modern Medicine*, Lea & Febiger, Philadelphia and New York, 1908, v, 458.

2. Holt, L. E.: *The Diseases of Infancy and Childhood*, D. Appleton & Company, New York and London, 1909, p. 353.

*Previous History.*—The child was born on November 15 at 3 p. m., after a normal, easy delivery. Vomiting began as soon as the child was put to the breast and was repeated after every feeding. The vomited matters were bile-stained mucus and milk. On account of the fact that the bowels did not move, on the following day calomel was given without result, and after an enema a small amount of inspissated meconium was passed. The vomiting continued until the child was brought to the hospital. Repeated enemata were given without result. The urine was normal.

The infant was put to the breast regularly and given about a dram of warm water after each feeding. All feedings were retained about four hours and then a small amount of milk was regurgitated. Three hours later it had another attack when about four ounces were vomited in somewhat of a projectile manner. Little vomiting attacks then continued at intervals and the child became fretful. The day following its birth the infant appeared dull, listless and was somewhat jaundiced. A loss of four ounces in weight was noted. There was



The bowel was fixed in a formaldehyd solution and then arranged so that an exact tracing could be made of its shape and length. This tracing was then photographed and the figure presents, on a smaller scale, the true relations of the stenosed and obstructed points. There were three compartments in the small bowel that were entirely closed at either end. Other points of stenosis were apparent at 5, 6, 7, etc., as indicated in the figure. The entire length of the small bowel was 175 cm., that of the large bowel 30 cm.

no bowel movement. Congenital obstruction was suspected and Dr. Herrick advised and performed a laparotomy. Exploration revealed a high congenital malformation causing complete obstruction of the small bowel, and other points indicating stenosis of the small intestine. Surgical interference appeared hopeless and further operative efforts were abandoned. The abdomen was closed and the child removed to the ward. Death occurred a few hours later.

*Necropsy.*—A small, male, white child; skin and conjunctiva jaundiced; head not examined. Nothing abnormal was found in the thoracic or any of the abdominal organs excepting the gastro-intestinal tract.

The stomach appeared normal but the peculiar formation and arrangement of the large and small bowel necessitated a careful removal and rearrangement before all segments could be recognized.

Four complete congenital occlusions of the small bowel were found. The first one was 28 cm. from the pyloric ring and the form of occlusion was that

of a thin tissue diaphragm lined on its upper surface by the usual type of mucous membrane, while below, it had a smooth parchment-like surface. The duodenum and the portion of the jejunum above this partition had been a large food reservoir for all the food taken, and therefore was tremendously dilated and the wall thickened. This portion of the bowel and that which immediately followed it were so modified in appearance that the first impression on opening the abdomen was that some peculiar transposition of the viscera had taken place, because it resembled a large cecum and appendix. This enlarged portion had gravitated to the right iliac fossa. Only a complete dissection of the esophagus, stomach and bowel allowed a proper orientation.

The second obstruction was found 15 cm. below the first one mentioned, but instead of a membranous partition the bowel simply tapered off to a fine solid cord of tissue measuring 3 or 4 mm. in length and about 1 mm. in diameter. No food had ever had access to this portion of the bowel. The content was a clear, mucous fluid.

The third obstruction was 10 cm. below the second one just described and was similar in nature.

The fourth obstruction was 42 cm. below the third and was a membranous partition like the first one described except that the segment of the bowel and the partition were of course small. On the peritoneal coat there was no evidence of this occlusion and even though the surgical intervention had removed the first, second and third obstructions, this one would have defeated their efforts. This point was found only by injecting water through a syringe into all portions of the bowel to see how many compartments really existed.

When water was injected above the first obstruction it eventually escaped through the stomach and esophagus and when injected below the fourth obstruction it escaped through the large bowel by way of a catheter in the rectum. No imperforate state of the ano-rectal region existed.

No evidence of a congenital malformation was found in the body other than a small, persistent foramen ovale.

The case not only presents an unusual number of congenital malformations in the jejunum but shows how difficult and hopeless surgical treatment may be under such conditions.

## INTESTINAL PARASITES IN CHILDREN \*

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The subject of intestinal parasites in children is one that I believe has not been given the care and attention that it rightly deserves. Generally speaking, only those patients are examined for parasites who come with a definite history referable to the parasites, such as the finding of a segment of tenia in the stools, or when the mother of the patient makes the statement that she believes that her child has worms, do we ask for a specimen and examine or have the stools examined.

That this was true was forcibly brought to my attention by the number of cases that came to me, both in my private practice and in the West End Dispensary, either with the statement by the mother that the child had worms, or with the child complaining of other symptoms not referable to a parasitic disease; yet on routine examination these cases were found to harbor one or more of the different parasites to be mentioned later.

Although the Rockefeller Hookworm Commission had as thoroughly and systematically worked the state by counties as was possible with funds and time available, I determined to study the subject through the children that came under my observation in my clinic, at the Masonic Home, and also through the courtesy of Dr. P. B. Moss, State Pathologist and Bacteriologist, the children under the age of 12 years who came to the State Pasteur Institute to be treated for dog bites.

My observations include all those children who were at the Masonic Home or who came to the clinic or Pasteur Institute, regardless of the nature of their complaints. Some of them, especially the cases from the Home and Pasteur Institute, did not complain of any untoward symptoms whatsoever. In fact, they were perfectly healthy specimens whose parents would never have thought to consult a physician had it not been for the accidental bite of a supposedly rabid dog and their fear of hydrophobia. These observations cover a period from Septem-

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ber, 1910, to March, 1915, in the Pasteur Institute, and from May, 1914, to April, 1915, in my own dispensary and Masonic Home. (The examinations were made in the State Laboratory by Dr. P. B. Moss or one of his assistants). The total number of children examined being 665, 80 of whom were negroes, and all under 12 years of age. Of this number 240 were found to be infected; 425 negative, or 36.1 per cent., of the children were found to harbor one or more of the varieties of parasites as follows:

Hookworms .....	177	(62 F. 115 M.)	26.75%
Hymenolepis nana .....	38	(20 F. 18 M.)	5.75%
Ascaris lumbricoides.....	27	(12 F. 14 M.)	4.06%
Oxyuris vermicularis.....	5	(3 F. 2 M.)	.75%
Trichocephalus dispar.....	5	(2 F. 3 M.)	.75%
Mixed infections 2 or more parasites..	12	(6 F. 6 M.)	1.8 %

*Amoeba coli* and *Amoeba histolytica* will not be considered here.

Of these infections it will be noted that three children of one family had a double infection of *Ascaris lumbricoides* and *Trichocephalus dispar*. In one family one child was infected with hookworm and *Hymenolepis nana* while the second had hookworm only. In the third family one child was infected with *Hymenolepis nana* and *Trichocephalus*. In still another, one child was infected with *Hymenolepis nana*, with both hookworm and *Hymenolepis nana* in the second.

It is a common occurrence to find whole families infected with hookworm, while in five families *Hymenolepis nana* was found in two or more members. In many cases it was only possible to examine one child of a family or I believe this number would be largely increased.

It is to be remembered that very few of these patients complained of any untoward symptoms due to the parasites, but as before stated, came to the Pasteur Institute to be treated for dog bites, or to the dispensary for any of the ordinary diseases that usually come to a dispensary or free clinic.

It might be well to mention here that of the patients presenting themselves to the Pasteur Institute 34.5 per cent. were infected. Many of them came from Birmingham, Mobile, Montgomery, Selma and the larger centers of population of the state where hookworm infection is not so common as in the rural districts and medical attention is much easier to obtain, and where had they complained of any symptoms referable to the parasites, they would more than likely have been discovered and treated.

Therefore, the percentage of intestinal parasites in children of the state as a whole may be considered even larger than have been found here.

The large percentage of parasites which apparently give no untoward symptoms might easily lead one to believe that they are of



little relative importance to the health of the child. That such is not the case I have proved to my own satisfaction by treating several children complaining of abdominal pains, loss of appetite, tired, listless feeling, etc., and giving them a thorough treatment, watching the marked improvement in the general condition and the disappearance of symptoms complained of. Especially was this so in some of the children of the Home. Several of these when admitted were pale, sallow, undeveloped, listless children with no appetite, and yet did not complain of any specific illness. Examinations of feces showed severe, neglected infection in some cases of more than one variety of parasite. They were first given a course of treatment for hookworm and allowed to rest from one to two weeks, when the feces were again examined; if they showed any infection they were given a second treatment. All that had showed signs of infection were re-examined in four weeks, and if necessary, treated again. It is my intention to have these children given a routine examination in six months and to repeat the treatment wherever necessary.

Although I have had these children in charge for over one year, since the eradication of the parasitic infection there has been very little illness at the home. Those who were infected, after treatment took on a different aspect. They lost their sallow complexion, regained appetite and became as other children.

I have made no effort to go into the etiology, symptomatology or treatment for these parasites, but to find out the percentage of children infected and the relative proportion of the different parasites found on routine examination.

It was not surprising to find hookworm to be by far the commonest of the infections, especially in this section, but the large percentage of *Hymenolepis nana* and *Ascaris lumbricoides* and the small number of *Oxyuris vermicularis* was somewhat of a surprise,<sup>1</sup> as the *Oxyuris* has been considered quite common, especially by the parents of the patients, while the *Hymenolepis nana* was considered comparatively rare.

There can be no doubt of the importance of ridding the children of these parasites, as they are undoubtedly a factor in the malnutrition and poor development of many, and may be a predisposing cause of pellagra, tuberculosis, dysentery, subacute and chronic appendicitis and other diseases. In thirty-five cases of pellagra under my care, thirty-one were infected with either hookworm, *Hymenolepis*, or both.

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1. This bears out Schloss in his article in Archives of Pediatrics, February, 1910.

The frequency of intestinal parasites when looked for, has been shown by other investigators. Still<sup>2</sup> found 32 parasitic infections in 100 consecutive autopsies. Schloss<sup>3</sup> found 11 per cent. of the children who came to his dispensary, infected with some variety of parasite. Wilson<sup>4</sup> reports twenty pinworm infections in 100 consecutive necropsies in children, and other reports bear this out. Although these investigations do not show such to be the case, McNeil<sup>5</sup> states that pinworm is comparatively common; that contrary to the general impression, they are usually found in the small intestine, cecum, and appendix, rather than in the lower intestine. In severe infections they may travel down to the anus and be detected there if searched for, but usually they are not found in the stools unless drawn down by an active purge, and even then an active search is necessary. McNeil<sup>5</sup> also states that it is pretty thoroughly demonstrated that both the pinworm and the whipworm are etiologic factors in attacks of acute and subacute appendicitis, and that they probably lay the foundation for some attacks of suppurative appendicitis.

The reduction of death rate in Bilibid prison from 75 per 1,000 to 9 per 1,000 after quarantining the persons harboring intestinal parasites, seems to indicate that there is some importance to be attached to their presence.

#### CONCLUSIONS

1. That parasitic infections in children are far more common than has heretofore been thought.

2. That while hookworm infection is the most often found, *Hymenolepis nana* and *Trichocephalus dispar* are by no means rare.

3. That less than 10 per cent. of the cases infected complain of symptoms referable to the infection.

4. That by routine examinations, many cases will be found otherwise unsuspected and by thorough treatment their general condition will be greatly improved.

5. Every county and municipality should appoint a physician for special work along this line, to follow the work done by the Rockefeller Hookworm Commission and under the direction of the state health officer, who should at frequent intervals examine the feces of every child in his district. No child should be permitted to attend a public or private school until after such an examination and the results prove to be negative.

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2. Still: Common Diseases and Disorders of Childhood.

3. Schloss: Am. Jour. Med. Sc., 1910, cxxxix, 458.

4. Wilson: Brit Med. Jour., 1913, p. 2676.

5. McNeil: Southern Med. Jour., June, 1915, p. 487.

## POLYCYSTIC DISEASE OF THE KIDNEY IN AN INFANT THREE MONTHS OLD \*

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According to Kelly, polycystic disease of the kidney occurs principally at two periods of life—before or immediately after birth, or after 40 years of age. Although many cases in adults have been reported in the literature, the disease is uncommon enough in infants to warrant the publication of the following instance as well as a brief discussion of the condition.

### CASE REPORT

*History.*—H. D., female, 3 months old, was admitted to the A. Jacobi Division for Children of the German Hospital, May 13, 1915. Forceps delivery. Weight at birth not known. Breast feedings were given every two hours. The mother has had no miscarriages. There is no family history of lues or tuberculosis. Both parents and one brother of the patient are alive and well.

*Present Illness.*—About two weeks after birth the mother noticed that the infant's abdomen began increasing in size. Shortly afterwards the physician who was called stated that the child had an enlarged liver. In the past two months the increase in the size of the abdomen has been progressive. There have been occasional attacks of abdominal pain, apparently most severe with the child on its back. Stools were three to four daily, and always contained mucus; blood was noticed on one occasion. Appetite has always been good. There has been no vomiting. At no time were there urinary symptoms. The urine has been dark colored at times, but the diapers were never stained. The general condition of the infant has been poor since the first month of life.

*Examination.*—On admission to the hospital examination showed a badly developed infant in a profoundly prostrated condition. Weight 10 pounds. Length  $22\frac{1}{2}$  inches (57 cm.); circumference of head  $14\frac{1}{2}$  inches (37 cm.); circumference of chest  $14\frac{3}{4}$  inches (36.5 cm.). The examination of the skin, eyes, ears, nose, mouth, throat, lungs and heart was negative. Very slight generalized enlargement of the lymph-nodes.

Abdomen: Markedly enlarged and distended. Circumference of abdomen at umbilicus 16 inches (40.5 cm.). A small umbilical hernia is present. In each flank a large, hard, somewhat irregular mass is palpable; the tumors extend from the costal arches into the pelvis. The inner margin of the mass on the right side feels lobulated, and appears to be continuous above with a mass extending transversely to the left and posteriorly below the costal margin.

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\* From the A. Jacobi Division for Children of the German Hospital, New York.

Both masses are ballottable from the flank. Dulness is present over each. The percussion note is tympanitic towards and in the median abdominal zone. There is no moveable dulness present, and a fluid wave could not be elicited.

Liver: The edge is palpable 3 inches below costal margin; its surface feels smooth and is not tender.

Spleen: Not felt.

Rectal Examination: Negative.

The von Pirquet reaction was negative. Roentgen-ray examination (Dr. W. H. Stewart) showed an enlarged abdomen and an hypertrophied heart (Fig. 1).



Fig. 1.—Polycystic disease of the kidney, showing hypertrophied heart.

The urine contained a very slight trace of albumin and a few granular casts. No red blood cells were present. The temperature, respiration and pulse rate were normal. The blood examination showed on admission: hemoglobin, 70 per cent.; white cell count, 13,200; polynuclears, 50 per cent.; lymphocytes, 46 per cent.; eosinophils, 4 per cent.

In the absence of a luetic history, and especially because the general condition of the patient was so poor, a Wassermann test was omitted.

The chief point of interest in this case was the presence of the bilateral tumor masses in the abdomen, with the history of the evolution shortly after birth. In an effort to arrive at the diagnosis the following possibilities were considered:

1. Tuberculous peritonitis.
2. Syphilis.
3. Sarcoma of omentum.
4. Sarcoma of kidney.
5. Polycystic disease of the kidney.

Tuberculosis and syphilis were ruled out because there was no specific history, and because the symmetrical arrangement of the tumors and their presence dating from birth, spoke against these conditions. A differential diagnosis between sarcoma of the omentum and kidney tumor (malignant or cystic) could not be definitely made. As will be indicated below, bilateral abdominal tumors in an infant dating from birth, with signs of chronic kidney inflammation and an hypertrophied heart, speak very strongly for polycystic disease of the kidney. Nevertheless a positive diagnosis could not be made.

In view of the fact that the tumors were gradually progressing in size, and that the infant's condition was gradually getting worse, an exploratory operation seemed advisable. At the laparotomy, performed by Dr. F. Kammerer four days after the patient had been admitted to the hospital, the tumor masses were found to be retroperitoneal, and in the position of the kidneys. The patient died the day after the operation.

We are indebted to Dr. F. B. Humphreys, pathologist to the German Hospital, for a detailed report of the necropsy findings. The following is an abstract from his records:

*Pathologist's Report.*—Heart: Weight 62 gm.; hypertrophied, but otherwise normal.

Lungs: Slight congestion; no enlargement of bronchial lymph nodes.

Thymus: Weight 7 gm.

Intestines: Slight congestion. The small intestine was distended, due to partial obstruction by the tumor masses.

Kidneys: (Figs. 2 and 3.) Enormously enlarged. The right kidney weighed 240 gm., and the left kidney 230 gm. Each kidney measured 12 by 6 by 5 cm. The organs were irregularly lobulated. The capsule was firmly adherent. The section was of a light yellow color streaked with coarse vertical white striae. There was scarcely any differentiation between cortex and medulla. The kidneys were of a spongy or boggy consistency, the meshes of the sponge being filled with a clear, light-yellow fluid which could easily be expressed. There were a few good-sized cysts (3 to 4 cm. in diameter) and innumerable smaller ones (pin point in size) scattered throughout the kidneys. The mucous membranes of the calices and pelves appeared normal.

Liver: Weight 235 gm. Normal in appearance, but of unusually firm consistency. On section the connective stroma was increased, the normal liver tissue being replaced by a firm white network resembling connective tissue. Small brown islands were enclosed in the latter.

*Microscopic Examination.*—Kidneys: Almost the entire parenchyma was made up of exceedingly irregular epithelium-lined spaces of varying sizes. No resemblance to the normal renal tubules was discoverable. The normal histologic landmarks were almost completely obliterated; glomeruli and nondilated tubules were found in isolated groups irregularly scattered in the connective tissue between the spaces. For the most part, however, the spaces were bare. The epithelial cells referred to were of the flattened cuboidal type, and were detached from the underlying basement membrane in many places. The connective tissue varied greatly in amount in different specimens. In most places

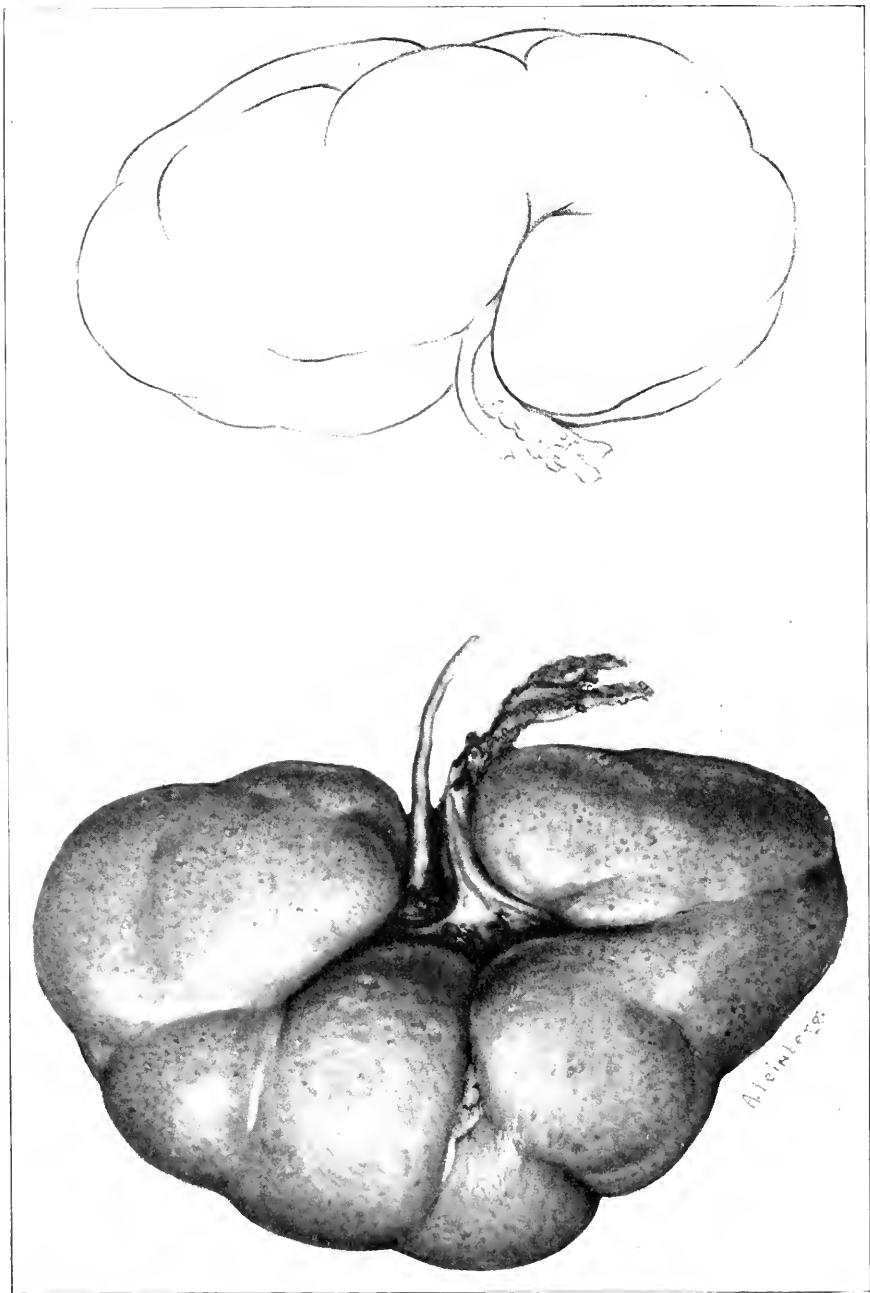


Fig. 2.—Polycystic disease of the kidney.

it was very scanty, serving only as a thin sheath for the capillaries between the dilated tubules. Imbedded in it were the approximately normal glomeruli and tubules. These areas were more numerous near the surface, where the stroma becomes continuous with the external capsule. There was no marked inflammatory reaction. Spirochetes were not found in section prepared by Levaditi's method.

Liver: The interlobular connective tissue was enormously increased in amount, its bulk approximately equaling that of the epithelial lobules. The latter were much reduced in size and formed irregular islands of varying sizes, separated by broad bands of connective tissue. There was no marked intra-lobular fibrosis, although there was pronounced congestion. The most remarkable feature was the hyperplasia, hypertrophy and dilatation of the bile ducts.

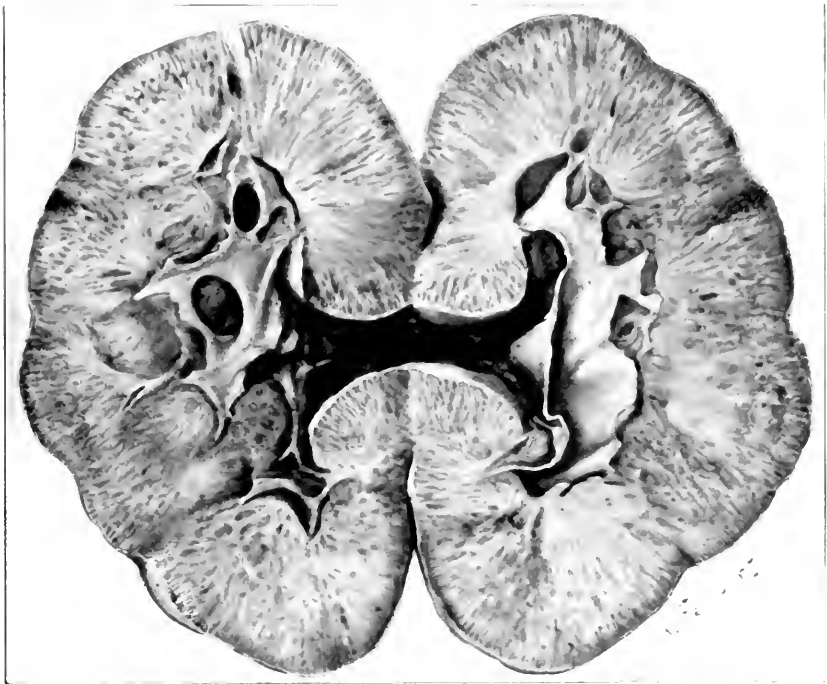


Fig. 3.—Polycystic disease of the kidney.

The interlobular connective tissue was everywhere honeycombed by large irregular intercommunicating spaces of varying sizes, lined by single rows of columnar epithelium resembling that of the normal bile passages. Some were empty; others, especially the larger ones, were filled with cellular detritus, pigment, etc. The surrounding connective tissue contained scattered areas of round cell infiltration, but showed no recent inflammatory changes. Silver nitrate impregnation after the method of Levaditi showed no spirochetes.

#### DISCUSSION

*Etiology.*—There are numerous theories concerning the etiology of cystic disease of the kidney. According to Moschcowitz the theory expounded by Virchow is the oldest one. Virchow maintained that

the cysts arose from an intra-uterine papillitis caused by irritation of uric acid and lime salts, resulting in atresia and obliteration of the collecting tubules. This is the so-called inflammatory or retention cyst theory, which has very few adherents at the present time.

Some years later, Brigidi and Severi maintained that cystic disease of the kidney bore distinct earmarks of tumor formation, and therefore termed it "multilocular adenocystoma." This view was upheld by many other observers, but it may in general be said that proofs of the neoplastic theory of cystic disease of the kidney have been lacking.

The theory which is now generally accepted was first suggested by von Mutach. He believed that cystic disease of the kidney was due to anomalies in the organ resulting in imperfect development. This theory is supported by the fact that other anomalies and malformations are often associated with this condition. According to Moschcowitz there is present a striking association between cystic disease of the kidney and congenital malformations in the genito-urinary system. Among the many other malformations often associated with cystic disease of the kidney the following may be mentioned: hare-lip, cleft palate, meningocele, spina bifida, absence of extremities, or polydactylism, hypospadias, atresia and absence of a ureter, double vagina, absence of bladder, imperforate anus, heart defects.

In about one-fifth of all cases of cystic disease of the kidney cysts in the liver and in other organs are encountered.

Although the great majority of modern writers are of the opinion that cystic disease of the kidney is always due to an error of development, some authors (Heimann, for example) still maintain that no one theory will fit all cases.

Heredity also plays a rôle in the etiology of this condition. Several cases of cystic disease of the kidney have been reported in members of one family. Males are more often affected than females. Most of the cases reported have occurred in adult life. A few cases have been observed in the new-born. Hardly any cases have been reported between the ages of 5 and 15.

*Symptoms.*—The symptoms of cystic disease of the kidney are dependent on the following: 1. Presence of the tumor masses. 2. Interference with kidney function. 3. Pressure. 4. Presence of malformations. Although in adults the kidney tumors may not reach huge proportions, they are at times enormously enlarged in infants. The enlargement may be unilateral or bilateral. The tumor masses are situated in the flanks, but owing to their progressive increase in size, they may reach from the costal margin to the pelvis, and centrally



to the median line. When large, the masses can be felt in the lumbar region. In the absence of marked intestinal distention the percussion note over the tumors is dull. Their surface is usually somewhat irregular, and their consistency firm. Owing to their small size and their diffusion throughout the kidney tissue, the cysts themselves can only rarely be felt. At times the enlargement of the kidneys is barely perceptible, but in these cases some fulness may be felt in the flanks, a fact of diagnostic importance.

Alteration in kidney function is invariable, but, since the urinary changes are often transient, it has been claimed that a normal urine may exist in this disease. The disturbed kidney function is shown by the presence of albumin, casts, and occasionally by blood in the urine. Although these findings may not be discovered at the first examination, repeated search will reveal them, especially when the disease is moderately well advanced. The phenolsulphonephthalein and other functional tests are also of value in this respect. Due to the accompanying nephritis, there may be, and there often is, increased arterial tension, and, with this, an hypertrophied heart. Where there is very extensive destruction of kidney tissue, the excretory function is so reduced that uremic convulsions and coma may ensue.

Pressure by the tumor is manifested either by the signs of intestinal obstruction or of renal colic. The latter results from the obstruction to the ureters, the former by pressure on the colon as it passes over the kidney. Intestinal obstruction has often been the cause of an immediate operation for its relief. Since polycystic disease of the kidney is in the category of congenital deformities, it is not rare to find other malformations present in this disease; when present they are therefore of some importance in the diagnosis.

*Diagnosis.*—The diagnosis of polycystic disease of the kidney is rendered extremely difficult at times by the absence of palpable enlargement of the kidneys; when only one organ is enlarged it may be mistaken for a renal neoplasm. The misplaced or greatly enlarged cystic kidneys may be confused with tumor growths of other viscera, the spleen or liver, for example. That the diagnosis is often overlooked is indicated by the frequency with which the condition is first discovered at the autopsy table, or at abdominal operations for other conditions. According to Preitz the following characteristics are diagnostic: 1. Palpable tumor mass. 2. Usually bilateral. 3. Irregular surfaces. 4. Accompanying cysts of the liver. 5. Typical deformity of the abdomen. 6. Diminished kidney function. 7. Uremic attacks. 8. Exploratory puncture. 9. Heredity. To these may be added: 10. Other malformations. 11. Hypertrophy of the heart. 12. Urine that shows the changes of a chronic nephritis.

As to the first of these signs, namely a palpable tumor, a survey of all the case reports will show that a mass was palpable in about 50 per cent. of the cases only, and a bilateral tumor very much more rarely. When only one kidney tumor is palpable, however, a fulness may sometimes be felt in the opposite flank, for in most cases, both kidneys are involved to a greater or less extent.

The surface of the tumor is usually irregular, and at times the tense fluctuating larger cysts can be determined by palpation. Liver cysts are too small to be of any value as a diagnostic sign. The abdominal deformity consists of an enlargement, and is not typical. Diminished kidney function cannot be accepted as a pathognomonic sign, for many patients live through adult life with large polycystic kidneys, and have an apparently normal urinary output. Uremic attacks occur late in the disease only, and are of no value in deciding on the condition. Exploratory puncture is out of the question on account of its danger. It is claimed that heredity is of value in the diagnosis, but in so few cases was a familial history present that not much stress can be laid on this point. The presence of other malformations is of some aid, for in many cases deformities of some kind have existed. They should, therefore, always be looked for. Cardiac hypertrophy is almost always present, the result of the nephritis with its high blood pressure.

*Of all the signs, therefore, most stress should be laid on the presence of a tumor either in one or both flanks accompanied by a nephritic urine, and an hypertrophied heart. In infants with these signs, especially if the tumors are bilateral, the presence of polycystic disease of the kidney is almost certain.*

*Prognosis.*—The prognosis of polycystic disease of the kidney varies with the individual case. At times, the disease has progressed so far in intra-uterine life that delivery is interfered with and the infant is born dead. Again, the infant may be born alive, but the tumor masses may be so large as to interfere with the infant's respiration and cause death. Some individuals, on the other hand, present absolutely no symptoms, and live to be 80 or 90 years of age. The prognosis, therefore, depends largely on whether one or both kidneys are affected, and on how much kidney tissue is functioning. The most favorable cases are those in which the chief involvement is confined to one kidney, and the opposite organ shows compensatory hypertrophy. In advanced cases death results suddenly with the symptoms of uremia or cerebral hemorrhage.

*Treatment.*—Medical treatment is entirely symptomatic. Nephrectomy should never be employed, inasmuch as both kidneys are usually

involved, and death ensues almost invariably. If the tumor masses are very large, and there is much pain and discomfort, multiple puncture of the larger cysts is indicated. This operation has been employed by Kammerer, Curtis, Rovsing, and recently by Lund with very favorable results. The size of the kidney is greatly reduced by this procedure, and much relief is afforded the patient. At times renal function is also much improved.

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# PROGRESS IN PEDIATRICS

## RECENT PROGRESS IN PEDIATRICS

### RÉSUMÉ ON THE CIRCULATION \*

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#### THE SIGNIFICANCE OF THE NORMAL ELECTROCARDIOGRAM †

The marked progress which has been made in recent years in the study of the pathology of heart function has been largely due to the introduction of the polygraph and the electrocardiograph, especially the latter. Until very recently, however, the exact significance of the various waves of the ventricular electrocardiogram has not been understood and the clearing up of this difficulty will undoubtedly add greatly to the usefulness of this instrument in the future. Lewis and his collaborators<sup>1, 2, 3, 4</sup> with the aid of the double string galvanometer have recently contributed a large number of new facts to this field. So far, the following things have been determined: The heart beat originates in the head or upper part of the sino-auricular node. From here the excitation wave spreads over the auricles in every direction, following the main muscle bundles, at a uniform speed of about 1,000 mm. per second.<sup>1</sup>

This wave reaches the ventricles after a period of from 0.12 to 0.17 second (in man), most of this time being consumed, according to the experiments of Hering,<sup>5</sup> in the passage of the wave through the node of Tawara. The excitation wave enters the ventricles by way

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† For the convenience of those not familiar with the electrocardiogram, the normal electrocardiogram of an adult with simultaneous venous pulse is shown in Figure 1. This electrocardiogram was taken in Lead II (right arm and left leg), and the sensitivity of the galvanometer was so adjusted that an ordinate of 1 cm. represents an electrical potential of 1 millivolt. The Q wave, as often happens, is not well developed in this electrocardiogram. In taking Lead I the electrodes are attached to the right arm and left arm, and in taking Lead III the left arm and the left leg are the extremities used.

1. Lewis, Meakins, and White: *Philosoph. Trans. Roy. Soc. Lond.*, 1914, Series B, ccv, 375.

2. Lewis, T.: *Lectures on the Heart*, 1915, New York.

3. Lewis, T.: *Proceedings Physiological Society*, March 13, 1915. Reported in *Jour. Physiol.*, 1915, xlix, No. 4, p. 20.

4. Lewis, T.: *Proceedings Physiological Society*, May 15, 1915. Reported in *Jour. Physiol.*, 1915, xlix, No. 5, p. 26.

5. Hering, H. E.: *Arch. f. d. ges. Physiol.*, 1910, cxxxi, 572.

of the His bundle and is very quickly distributed to the endocardial surface of both ventricles by the Purkinje fibers. The speed of the wave along these special structures is very rapid, being approximately 2,000 mm. per second. The excitation wave reaches the epicardial surface of the ventricles by passing out through the ventricular walls in a direction at right angles to the endocardial surface of the muscle at the comparatively slow speed of 400 mm. per second.<sup>2</sup> Since the wave reaches all points on the endocardial surface at about the same time, it will be seen that the time of its appearance at any point on the external surface of the ventricles will depend on the thickness of the muscle at this point, and the excitation wave will appear first where the muscle is thinnest. It is this first spread of the excitation

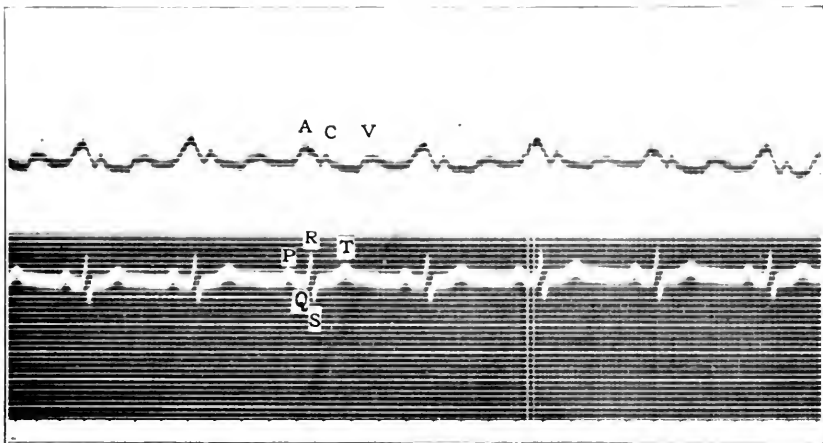


Fig. 1.—Lead II. In this as in the following figures, an ordinate of 1 cm. is equal to 1 millivolt. A normal electrocardiogram with simultaneous venous pulse. The P wave of the electrocardiogram and the *a* wave of the venous pulse represent auricular contraction. All other waves represent ventricular contraction.

wave over the ventricles which is responsible for the QRS group of the electrocardiogram and the configuration of this group of waves therefore depends largely (if we disregard the effect of the position of the heart, the derivation, etc.) on the distribution of the ventricular muscle. It is for this reason that the QRS group is so profoundly modified by the preponderance of the one or the other ventricle.

Lewis<sup>3, 4</sup> has also shown that the ventricular electrocardiogram is a bigram, and that it is formed by the algebraic summation of the right ventricular electrocardiogram (dextrogram) and the left ventricular electrocardiogram (levogram). The dextrogram and the levogram of the monkey, in which animal the heart structure closely approaches that of man, correspond very closely to the clinical curves

which have been regarded as characteristic of left and right bundle-branch block, respectively (Figs. 2 and 3). In other words, the dextrogram is diphasic and the initial deflection is directed downward in Lead I and upward in Lead III, and the levogram is similar except that the direction of the initial deflection in these leads is reversed. These facts indicate that in Lead III Q and S are due to left and R to right ventricular effects (Figs. 2 and 3), while in Lead I the opposite is true. The significance of the T wave is as yet less perfectly understood.

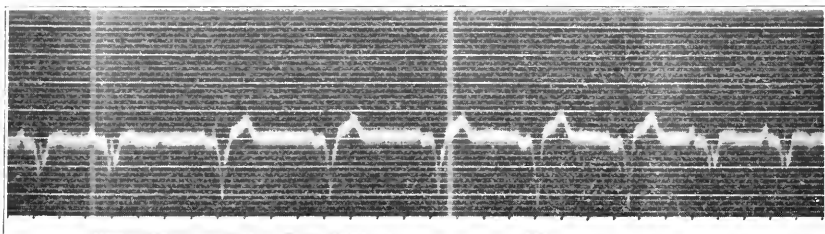


Fig. 2.—Lead III. A gradual transition from ventricular complexes of the normal type to ventricular complexes characteristic of a block in the right branch of the His bundle. The R wave of the normal complex, which is due to right ventricular effects, gradually disappears as the block becomes more marked. An A-V rhythm of Type 1 (see Fig. 4) was present during the branch block.

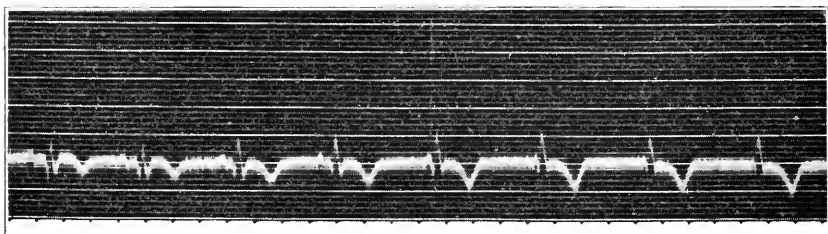


Fig. 3.—Lead III. From the same patient as the previous figure. A gradual transition from ventricular complexes of nearly normal outline to ventricular complexes characteristic of a block in the left branch of the His bundle. The Q and S waves of the normal complex, which are due to left ventricular effects, gradually disappear as the block becomes more marked. An A-V rhythm of Type 2 (see Fig. 5) was present during the branch block.

#### THE NORMAL ELECTROCARDIOGRAM OF THE CHILD

The normal venous pulse of the child does not differ greatly from that of the adult. A similar statement can not be made, however, in regard to the electrocardiogram. According to Hecht,<sup>6</sup> the electrocardiograms of nurslings are absolutely smaller than those of older

6. Hecht, A. F.: *Ergebn. der inn. Med. u. Kinderh.*, 1913, xi, 324.

children and in addition to this there are other differences which will be discussed in order.

*The S Wave.*—In nurslings the S wave of the electrocardiogram was found to be unusually prominent by Funaro,<sup>7</sup> by Heubner,<sup>8</sup> and by Funaro and Nicolai.<sup>9</sup> This large S wave became gradually smaller during the first year of life. Hecht<sup>6</sup> examined a large number of children with the electrocardiograph and was able to confirm the observations of these authors. He found that in Lead I the S wave of the electrocardiogram of the new-born infant was on the average three times as large as the R wave. In adults the S wave is relatively only one-tenth as large. The S wave of Lead II was also exaggerated, but less than that of Lead I. In both leads the S wave decreased in size as the child grew older. Hecht believes that the unusual prominence of the S wave in early infancy is not due to the high diaphragm of this period of life, as supposed by other authors<sup>7, 8, 9</sup>; but to some peculiarity of the infant's heart. Lewis<sup>10</sup> has also investigated this subject using all three leads. His results were similar to those obtained by other observers, but he pointed out that the electrocardiograms of the new-born correspond to those obtained in adults with hypertrophy of the right ventricle. He believes that the prominent S waves of Leads I and II during early infancy is due to the preponderance of the right ventricle during this period. According to this observer, the electrocardiogram changes to the adult type between the second and third months of extrauterine life.

*The Q Wave.*—Hecht<sup>6</sup> found also that the Q wave was more frequently present in the electrocardiogram of the new-born than in that of older children. In his series of cases, this wave never occurred in Lead I, occurred occasionally in Lead II, and was frequently present in Lead III. It seems likely that this peculiarity of the electrocardiogram of the infant is also due to right ventricular preponderance.

*The P-R Interval.*—Kent<sup>11</sup> has shown that the As-Vs interval in young animals is shorter than in adults and according to Hecht<sup>6</sup> the same is true of man. He found that the P-R interval increases gradually from infancy to puberty. At birth and during the nursing period it averages 0.10 second in duration, during the early years 0.13 second, and at puberty 0.14 second. In adults the normal P-R interval varies from 0.12 to 0.17 second.<sup>12</sup>

7. Funaro: Riv. di clinica paediat., 1910, viii, No. 6. Quoted by Hecht, Note 6.

8. Heubner: Monatsschr. f. Kinderh., vii, 1. Quoted by Hecht, Note 6.

9. Funaro and Nicolai: Quoted by Hecht, Note 6.

10. Lewis, T.: Clinical Electrocardiography. London, 1913.

11. Kent, A. F. S.: Quoted by Hecht, Note 6.

12. Lewis, T.: Mechanism of the Heart Beat. London, 1910.

## THE VAGUS NERVES AND RESPIRATORY ARRHYTHMIA

*Effect of the Vagus Nerves upon the Pace-Maker.*—The researches of Eyster and Meek<sup>13, 14</sup> and of Lewis and his collaborators<sup>1, 15</sup> have added considerably to our knowledge of the influence of the vagus nerves on the heart. These authors have found that the slowing of the heart which is produced by stimulation of the vagi is accompanied in dogs by a downward displacement of the pacemaker within the sinoauricular node.<sup>1, 14</sup> Occasionally, the displacement of the pacemaker is still more marked and vagus stimulation produces an atrio-ventricular rhythm.<sup>13, 15</sup> Clinically also, an A-V rhythm may appear as a result of vagus stimulation<sup>16, 17</sup> and it is possible that this sometime occurs in children.<sup>18</sup> It is probable that the appearance of A-V rhythm on stimulation of the vagus nerves is due, in these instances at least, to the fact that, as has been shown by Eyster and Meek,<sup>19</sup> the vagus nerves exert more of an inhibitory effect on the sinus node than on the A-V node. According to these authors the inhibitory effect of the vagi upon the various centers in the system of specialized tissue found in the heart diminishes as we move from the sinus node downward.

*The Oculocardiac Reflex.*—The oculocardiac reflex in children has been investigated by Gunson.<sup>18</sup> The afferent path of this reflex lies in the fifth cranial nerve, the efferent path in the vagi most often, but occasionally in the sympathetic system. The reflex is considered positive when ocular pressure slows the heart. Gunson's series of cases included fifty cases of diphtheria and twenty-five cases of scarlet fever. The reflex was positive in 92 per cent. of the patients convalescent from these diseases. It was negative in 8 per cent. and was often negative when the heart was rapid during the period of pyrexia. It was also negative in patients with gallop rhythm, cardiac dilatation, hepatic enlargement, and marked arrhythmia—a syndrome which is termed "cardiac paralysis." In some of the cases in which the reflex was positive he observed complete inhibition of the heart for as long as four seconds, reduction of the a-c interval due to A-V rhythm or escape of the ventricles, and complete dissociation of auricles and ventricles. The last was observed in cases of diphtheria only.

*Respiratory Irregularity.*—Hecht<sup>6</sup> has shown that the respiratory irregularity which is physiologic and practically universal in children,

13. Eyster and Meek: *Heart*, 1914, v, 227.

14. Meek and Eyster: *Am. Jour. Physiol.*, 1914, xxxiv, 368.

15. Lewis, T.: *Heart*, 1914, v, 281.

16. Wilson, F. N.: *Arch. Int. Med.*, 1915, xvi, 86.

17. Gallavardin, Dufourt, and Petzetakis: *Arch. d. mal. du coeur*, 1914, vi, 1.

18. Gunson, E. B.: *Brit. Jour. Child. Dis.*, 1915, xii, 97.

19. Eyster and Meek: *Am. Jour. Physiol.*, 1915, xxxvii, 177.



becomes more marked from birth to puberty; that is, the difference between the shortest and the longest pulse period gradually increases as the heart rate decreases. The dependence of the grade of the arrhythmia on the heart rate can be shown by dividing a group of children of nearly the same age into two classes, those with rapid and those with slow heart rates. It will then be found that the respiratory arrhythmia is more marked in the second than in the first class. The average difference between the shortest and the longest pulse period at various ages, measured in fiftieths of a second, is shown in the following table taken from Hecht's recent monograph:<sup>6</sup>

At birth.....	3.4	Young children.....	6.25
Nurslings .....	2.8	Older children.....	8.4
Prematurely born.....	2.5		

#### ATRIOVENTRICULAR RHYTHM

Atrioventricular rhythm, formerly considered very rare, has been found quite frequently in recent years, often during the course of one of the acute infectious diseases, especially diphtheria. The presence

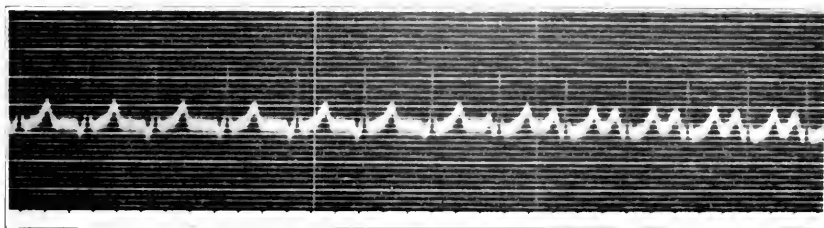


Fig. 4.—Lead II. A transition from an A-V rhythm of Type 1 to the normal rhythm. During the A-V rhythm P is inverted and the As-Vs interval is markedly reduced.

of this rhythm is recognized from polygraphic tracings by a reduction of the a-c interval. The gradual reduction of this interval which is seen when transitions between the normal and the abnormal rhythm are graphically obtained is especially characteristic. In the electrocardiogram, the presence of an atrioventricular rhythm is recognized by the reduction of the P-R interval and the inversion of P in Leads II and III when this wave is not buried in the ventricular complex so that it is not separately distinguishable. There are three types of A-V rhythm, depending on the level within the junctional tissues at which the abnormal rhythm originates. In the first type (Fig. 4) the P-R interval is present, but reduced; in the second type (Fig. 5) the P-R interval is zero, and in the third type (Fig. 6) there is an R-P interval. The last two types can not be distinguished one from the other by polygraphic tracings since the simultaneous contraction of auricles and ventricles which takes place in both types causes a single

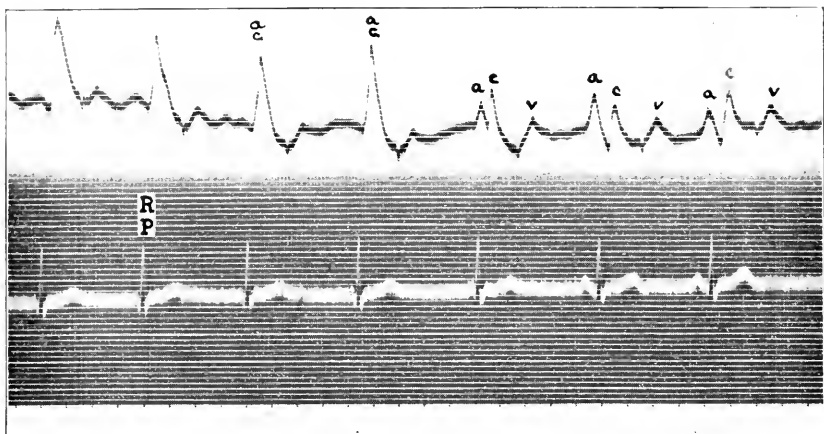


Fig. 5.—Lead II. A transition from an A-V rhythm of Type 2 to the normal rhythm. During the abnormal rhythm the P-R interval is zero and P is not visible, as it is buried in the ventricular complex. The *a* and *c* waves cannot be separately distinguished in the venous pulse during the A-V rhythm. At the end of this rhythm the change in the length of the a-c interval is gradual.

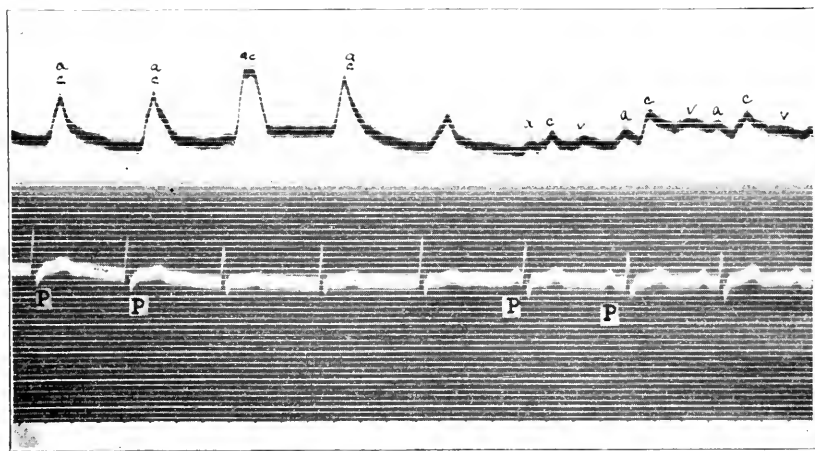


Fig. 6.—Lead II. A transition from A-V rhythm of Type 3 to the normal rhythm. During the abnormal rhythm P falls just after R and is inverted. At the end of the A-V rhythm auricular and ventricular contractions gradually return to their normal time relationship. As long as auricles and ventricles contract simultaneously, there is a large composite wave in the venous pulse, but the auricular and ventricular elements of this wave are not separately distinguishable.

large wave in the venous pulse (Figs. 5 and 6) which is due to the fact that the auricles being unable to force their blood into the ventricles, since the auriculoventricular valves are closed, force it back into the veins. It is impossible to separate the auricular and the ventricular elements in this large wave and so estimate the time relationships of the contractions of auricles and ventricles.

Atrioventricular rhythm has been observed in children suffering from diphtheria by Rohmer,<sup>20</sup> Hume,<sup>21</sup> and others, in cases of typhoid, scarlatina, and rheumatic fever by Belski,<sup>22</sup> and in cases of acute endocarditis by Cowan, Fleming, and Kennedy.<sup>23</sup> Since in most of the above cases only polygraphic tracings were taken, it is impossible to tell what type of A-V rhythm was present but it seems likely to me from an inspection of the tracings published that Type 2 was the most frequent. The exact cause of the appearance of atrioventricular rhythm in such instances is not certain. It seems possible, however, that it is due in some instances to inflammatory lesions of the sinus node which interfere with its function, since in two of Hume's cases which showed this rhythm, inflammatory changes were found in this node at necropsy. In both cases the A-V node and bundle were found to be practically normal. Another possible cause for the appearance of A-V rhythm, however, may be pointed out. I<sup>24</sup> have been able to show that the heart shows an unusual tendency to develop this rhythm during a certain period after the administration of atropin, and possibly other toxic substances may act in a similar manner. Atropin seems to produce this tendency toward A-V rhythm by a selective action on the fibers of the vagi which go to the junctional tissues.

#### HEART BLOCK IN CHILDREN

*Occurrence.*—Three types of heart block have been observed in man, sino-auricular block, A-V bundle branch block, and auriculoventricular block. So far as I know, the first two types have not yet been observed in children. Auriculoventricular block, however, is not uncommon in childhood. It has been observed frequently in acute rheumatic fever and in diphtheria, and less often in influenza and other acute infectious diseases. Syphilis, which is a common cause of heart block in adults, seems infrequently or never to produce this condition in children.<sup>6</sup> That heart block may occur in some of the acute infectious diseases without any accompanying structural changes in the A-V bundle has been shown by two fatal cases of diphtheria, one

20. Rohmer, P.: *Jahrb. f. Kinderh.*, 1912, lxxvi, 391.

21. Hume, W. H.: *Heart*, 1913-14, v, 25.

22. Belski: *Ztschr. f. klin. Med.*, 1909, lxxvii, 515.

23. Cowan, Fleming, and Kennedy: *Lancet*, 1912, i, 277.

24. Wilson, F. N.: As yet unpublished.

reported by Price and MacKenzie<sup>25</sup> and the other by Hume,<sup>21</sup> in which heart block was present although the A-V bundle was negative at necropsy in each case.

Digitalis in large doses may produce heart block in children<sup>6, 26</sup> as well as in adults, especially if the conductivity of the His bundle be somewhat impaired before the drug is given. Hecht<sup>6</sup> reports a case of heart block in a patient, aged 15 years, with hydrocephalus, and thinks it possible that in this instance the block was due to stimulation of the vagus center by the increased intracranial pressure. Atropin was given and produced a ventricular arrhythmia but did not remove the complete A-V dissociation present.

Whipham<sup>26</sup> has recently reported two interesting cases of heart block in children with congenital heart lesions. The first child observed was 2 years and 2 months old. The heart was enlarged to the right and was globular in shape. There was a loud systolic murmur on auscultation. The pulse rate varied from 48 to 80 and the electrocardiograms showed that a 2-1 block was present. The child had a marked polycythemia, 8,400,000 red cells per c.mm. of blood, and a hemoglobin of 110 per cent. The second patient was a girl, aged 12 years, who had had measles but no other illnesses. She complained of precordial pain on exertion. There was no cyanosis. The pulse rate varied from 50 to 60 per minute and the electrocardiograms showed on some occasions complete block, while on other occasions the block was 2-1, 3-2, and mixed. The clinical diagnosis in each case was incomplete ventricular septum.

*The Effect of Atropin.*—Hecht<sup>6</sup> has reported some interesting observations on the effect of atropin on heart block in children. A 2-1 heart block in a child, aged 3 years, who was suffering from measles complicated by a secondary infection (influenza?) and who had received small doses of digitalis, was completely removed by the injection of atropin (0.0006g). A heart block in a child of like age with diphtheria was, however, not at all affected by this drug. The heart block was transient in the first case while in the second it was still present four months after the first examination.

A third case is still more interesting. The patient was a child, aged 5 years, with measles and influenza. Electrocardiograms showed complete heart block to be present. The idioventricular rate was 47 and the auricular rate 100. The child was given 1 mg. of atropin, which did not remove the block but increased the ventricular rate to 90 and the auricular to 142 per minute. Hecht believes that in this

25. Price and Mackenzie: Heart, 1911-12, iii, 203.

26. Whipham, T. R.: Proc. Royal Soc. Med., Nov. 27, 1914. Reviewed in Brit. Jour. Child. Dis., 1915, xii, 11.

case atropin increased the idioventricular rate by removing the inhibitory effect of the vagi on the ventricular center. So far as I know, a similar result has not been previously obtained by the administration of atropin in cases of complete heart block, and it has been well established that as a rule the idioventricular rhythm in this condition is not under vagus control. It has been suggested that the reason for this is that the lesion which destroys the muscular fibers of the A-V bundle also interrupts the nervous connection between auricles and ventricles.<sup>27</sup> It is also possible that whether or not the vagus nerves have any effect on the idioventricular rhythm depends on the level within the junctional tissues at which this rhythm originates.<sup>27</sup>

*Stokes-Adams Attacks.*—Another case of heart block is reported by Hecht<sup>6</sup> in a child, aged 9 years. The block appeared after an attack of valvular endocarditis and was complete. The patient had attacks of unconsciousness and fainting spells, which were probably Stokes-Adams attacks. The ventricular rate was 40 and the auricular rate varied from 90 to 103. Hecht pointed out that in this, as in some of his other cases of complete heart block, the interauricular period was always shorter whenever a ventricular contraction fell between the two auricular contractions. The ventricular complexes of the electrocardiogram in this case were abnormal and resembled closely those seen when there is a block in one branch of the His bundle.

#### PREMATURE BEATS

Although according to Lewis<sup>25</sup> premature beats make up about 35 per cent. of the irregularities encountered in patients between adolescence and old age, they are very uncommonly found before the end of the first decade. When they do occur at this period of life it is usually in the course of some of the acute infectious diseases or in patients with evident cardiac disease. In children, premature beats arising in the auricles are apparently much more common than those arising in the ventricles, while the reverse is true in adults. Gunson<sup>29</sup> examined with the polygraph 120 cases of diphtheria and found auricular extrasystoles in 28 per cent., while ventricular extrasystoles were not observed in any of the cases. In the mild and moderately severe cases the extrasystoles were not associated with other signs of cardiac involvement, and were ignored in treatment. In five severe cases the extrasystoles were very numerous and there were signs of cardiac decompensation with gallop rhythm. Three of these patients

27. Zander, E.: *Nordisches med. Arch.*, 1915, ii, No. 6, Part 2. Reviewed in *Zentralbl. f. Herz u. Gefässkrank.*, July 1, 1915, p. 194.

28. Lewis, T.: *Clinical Disorders of the Heart Beat*. London, 1913.

29. Gunson, E. B.: *Brit. Jour. Child. Dis.*, 1914, xi, 385.

died. Atrioventricular extrasystoles are rare at all ages. They have been observed in children by Gunson,<sup>29</sup> Lewis and Allen,<sup>30</sup> Hume,<sup>21</sup> and others. Premature beats tend to be abolished by fever or anything which increases the heart rate.

The significance of extrasystoles is still in dispute. Visco<sup>31</sup> observed extrasystoles 48 times in a series of 1,000 observations on healthy and sick children, twice in normal children, 18 times in digestive disturbances and infections, once after the taking of belladonna, 14 times in dyscrasias, 3 times in epilepsy, 10 times in convalescents and patients with diseases of the skeleton. He thought they had very little significance. The experience of Hecht<sup>6</sup> and others, however, does not agree with this conclusion. Extrasystoles are much more serious when they occur before the tenth year and after middle age than they are when they occur during the intervening period of life. They are also more serious when they occur in patients with other signs of cardiac disease than when such signs are absent. Extrasystoles, as such, are of little moment unless they are so numerous as to cause circulatory embarrassment, which is infrequent, and they require no special treatment. They are sometimes, however, the precursors of more serious disorders of the cardiac mechanism and they may also indicate involvement of the myocardium.

#### AURICULAR TACHYSYSTOLE

Paroxysmal tachycardia of auricular origin and auricular flutter are very similar conditions. We are dealing in each case with very rapid coördinated auricular systoles and in each case these auricular contractions are ectopic in origin; that is, they arise outside the sino-auricular node. In adults the two conditions differ from each other in three particulars. First, in paroxysmal tachycardia the auricular rate is as a rule below, in auricular flutter above, 200 per minute. Second, in paroxysmal tachycardia the ventricular rate is the same as the auricular, while in auricular flutter, probably because of the extremely rapid rate of the auricular contractions, there is usually some heart block, so that the ventricular rate is a simple fraction of the auricular. When the patient first comes under observation the block is most often 2 to 1 so that the ventricles contract only one-half as many times as the auricles. Third, although in each of the two conditions the attacks of abnormal heart mechanism begin and end suddenly, the attacks of auricular flutter are as a rule much more persistent than attacks of paroxysmal tachycardia, their duration being

30. Lewis and Allen: *Am. Jour. Med. Sc.*, 1913, cxlv, 667.

31. Visco: Quoted by Hecht, Note 6.

measured in months or years rather than in hours or days. The administration of digitalis, which is the proper treatment in auricular flutter, after first increasing the heart block, often transforms this condition into auricular fibrillation. Later when this drug has been discontinued the normal heart mechanism may return. Digitalis is not often given in paroxysmal tachycardia because the attacks are usually short and require comparatively little treatment, and the production of fibrillation is inadvisable.

Both auricular flutter and paroxysmal tachycardia have been observed in children, but there is some confusion as to the separation of the two conditions at this period of life. The reason for this is that in children the auricular rate may often exceed 200 per minute without any block being present, and moreover, the attacks of very rapid auricular action so far observed in children have all been of comparatively short duration. We shall not attempt to distinguish between the two conditions, therefore, in this article, but shall refer to both as auricular tachysystole, giving the main features of the heart mechanism in each case mentioned.

Hutchinson and Parkinson<sup>32</sup> report a case in a child aged  $2\frac{3}{4}$  years. The first attack lasted until the twelfth day and was accompanied by edema of the face, the general appearance being similar to that seen in acute nephritis, and by edema of the legs and marked oliguria. There were three subsequent attacks lasting from 12 to 48 hours which were not accompanied by signs of cardiac decompensation other than enlargement of the liver. The heart rate varied from 212 to 245 per minute. One attack stopped when the child vomited and another shortly after defecation. The electrocardiograms taken during the attacks are decidedly abnormal and difficult of interpretation. It seems to me possible from an inspection of the tracings that the paroxysms were of ventricular origin. No premature beats were observed between attacks and the cause of the condition could not be determined. The usual heart rate between paroxysms was 84 to 105 per minute. The authors mention five other cases of "paroxysmal tachycardia" in children reported in the literature.

Kidd<sup>33</sup> has reported a case of "paroxysmal tachycardia" in a child, aged  $4\frac{1}{2}$  years. In one attack which lasted five days the heart rate was continuously 240 per minute and there were definite signs of cardiac decompensation. About one year after this attack the patient was again admitted to the hospital with a pulse rate of 150, and marked dulness to the right of the sternum, and enlarged liver. The pulse rate

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32. Hutchinson and Parkinson: *Brit. Jour. Child. Dis.*, 1914, xi, 241.

33. Kidd, P.: *Proc. Royal Soc. Med.*, Feb. 24, 1914. Reviewed in *Brit. Jour. Child. Dis.*, 1914, xi, 264.

varied from 80 to 240 and six months later the patient died with severe cyanosis and rapidly developing edema, the heart condition having remained the same in the interim.

Hume<sup>21</sup> has reported a case of "paroxysmal tachycardia" in a child, aged 6, with diphtheria. On the forty-first and fifty-first days of the illness short periods of tachycardia were recorded with the polygraph. The child was vomiting and in a grave, collapsed condition. The author thinks it probable that the attacks originated in the junctional tissues. They did not continue and the patient recovered. In a second case of diphtheria reported by the same author<sup>21</sup> the polygraphic tracings were not convincing but were interpreted as indicating that the auricles were contracting at a rate of 500 per minute while the ventricles were beating only one-fifth as fast. At autopsy a marked myocarditis was found to be present, the auricular muscle showed fatty degeneration, and the ventricles a marked interstitial inflammation with degeneration of the muscle fibers.

Sutherland<sup>34</sup> has recently reported two cases of auricular tachysystole in children with acute rheumatic carditis. The first patient was a girl, aged 8 years. The auricles, as shown by polygraphic tracings, were contracting at a rate of 280 while the ventricles were contracting only one-half as fast. The heart rate after the attack was 105. The second patient was a girl aged 6 years. In one attack the auricles were contracting at a rate of 250, while the ventricular rate was 125. Later an attack was observed in which the auricular rate was 390, the ventricular rate 130. Pulsus alternans was present at this time. Both patients had well marked signs of cardiac decompensation and the second patient died. Sutherland suggests that the presence of any of the following conditions in children indicates that the heart mechanism should be examined by graphic methods: 1. Attacks of cardiac asthma occurring suddenly and without any accompanying variations in the cardiac condition. 2. A triple or galloping or cantering rhythm heard on auscultation. 3. Pericarditis without effusion and with great respiratory distress. 4. Dyspnea, cyanosis, and enlargement of the liver out of proportion to the physical signs of disease of the heart. 5. The presence of pulsus alternans.

From an analysis of the above mentioned cases it will appear that auricular tachysystole in children is often of serious import and is usually accompanied by signs of cardiac decompensation, especially increase in the size of the liver. The symptoms and signs and the seriousness of the condition depend largely on the duration of the attacks and on the underlying causative factor. Lewis reports a case

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34. Sutherland, G. A.: *Brit. Jour. Child. Dis.*, 1914, xi, 337.



in an infant in whom the ventricular rate remained at 270 to 290 for several hours without the child apparently suffering any ill effects. According to this author such rates are exceptional and are only tolerated without grave circulatory embarrassment when the heart muscle is sound. High auricular rates have per se little significance if the ventricular rate remains low.

#### AURICULAR FIBRILLATION IN CHILDREN

While auricular fibrillation is a common clinical condition in adults comprising, according to Lewis'<sup>28</sup> statistics, 40 per cent. of the disorders of the heart beat encountered in an ordinary hospital practice, it is a very rare condition in children. In 1912 Price and Mackenzie<sup>25</sup> reported a questionable case of auricular fibrillation in a child with diphtheria. Complete heart block was also present. More recently three cases of auricular fibrillation during childhood have been recorded. Rheumatic fever was the most probable causative agent in each case.

Sutherland and Coombs<sup>35</sup> observed auricular fibrillation in a child, aged 5 years. The patient became ill suddenly and died after five days. At necropsy the myocardium showed very intense fatty metamorphosis, especially marked in the right auricle, and a very marked inflammatory reaction consisting of proliferative changes and infiltration with endothelial cells. The vascular reaction was marked and there was thrombosis of many of the fairly large vessels. The diagnosis made from the character of the illness and the autopsy findings was acute rheumatic carditis. Polygraphic tracings were published and there can be little doubt of the presence of auricular fibrillation, although electrocardiograms were not taken.

Ehrenreich<sup>36</sup> reports a case of auricular fibrillation in a child, aged 11 years. There was an indefinite history of rheumatism with a history of frequent attacks of cardiac decompensation since the age of 9. Examination showed marked dilatation of the heart, a double mitral murmur, and accentuation of the pulmonic second sound. Auricular fibrillation appeared under digitalis treatment during an attack of cardiac decompensation. Both polygraphic and electrocardiographic tracings were obtained, but these are not published.

A third case of auricular fibrillation was reported by Nadel.<sup>37</sup> The patient was a boy of 11 years of age who had had repeated attacks of rheumatic fever and several periods of broken compensation which

35. Sutherland and Coombs: *Heart*, 1913-14, v, 15.

36. Ehrenreich, S. G.: *New York Med. Jour.*, 1914, xcix, 269.

37. Nadel, V.: *Mitteil. d. ges. f. inn. Med. u. Kinderh.*, Wien., 1914, xii, 210. Reviewed in *Ztschr. f. Kinderh.*, 1914, viii, 88.

always reacted to treatment. The usual cardiac mechanism was normal except that the electrocardiograms showed an unusually large P summit and a P-R interval of 0.2 second, indicating hypertrophy of the auricular muscle and a slight degree of A-V heart block. Under digitalis treatment for cardiac decompensation, a 2-1 heart block developed and a bigeminy of the extrasystolic type also appeared. Later there was complete heart block with auricular fibrillation, and finally the block became less marked so that the ventricles responded irregularly to the fibrillating auricles. Electrocardiograms taken at this time showed that ventricular extrasystoles were frequent.

In conclusion we may say, therefore, that auricular fibrillation in children is a rare but grave disorder. The treatment is the same as for auricular fibrillation in the adult.

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## DUODENAL ULCER IN INFANCY AN INFECTIOUS DISEASE \*

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Since the publication<sup>1</sup> of the first large series of cases of duodenal ulcers in infants in 1909, numerous reports from various clinics and hospitals have appeared which have substantiated the frequent occurrence of duodenal ulcers in infancy. In 1913, Holt<sup>2</sup> collected ninety-one cases from the literature and added four more from his clinic. Since that time there have been numerous other publications on the subject which have increased the number of cases reported in the literature, but have not materially enriched our knowledge of the subject. Practically all the publications pass over the etiology of the ulcers with merely a reference to the usual explanations of the incidence of the ulcers as given in the textbooks of pathology (Holt,<sup>2</sup> Veeder<sup>3</sup>).

The etiology of gastric and duodenal ulcer is still a much debated question, so that any information as to its mode of incidence is of value. A very important point in the consideration of the etiology of the ulcers that has hitherto been overlooked is the fact that they have appeared in epidemic form, large series of cases occurring in a relatively short period of time. For example (1), in the first series of cases reported by one of us<sup>1</sup> in 1909, twelve cases were observed during the last four months of 1908, at the Berliner Kinder Asyl. In the first eight months of 1908, and in the entire year 1909, there were no further cases of ulcers observed at the Asyl. (2) Of his four cases Holt<sup>2</sup> says "Curiously three of these cases were observed within a period of three months." The fourth case was the only other one in a series of 1,800 necropsies. It can be added at this point that unless especially looked for, these ulcers are easily overlooked; but even if a

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\* From the Otho S. A. Sprague Institute Laboratory of The Children's Memorial Hospital.

1. Helmholtz, H. F.: Duodenal Geschwüre und Pedatrophie, Deutsch. med. Wehnschr., 1909, i, 534.

2. Holt, L. E.: Duodenal Ulcer in Infancy, AM. JOUR. DIS. CHILD., 1913, vi, 381.

3. Veeder, B. S.: Duodenal Ulcer in Infancy, Am. Jour. Med. Sc., 1914, cxlviii, 709.

few were overlooked in this series, the grouping of cases still remains very evident. (3) During seven months from September to April, we observed at this hospital eleven cases of duodenal ulcer. These eleven cases represent the only cases of duodenal ulcer that have been observed at our hospital.

This grouping of cases suggests very strongly that we are dealing with an infection and that we must seek for an explanation that will account for the epidemic-like appearance of ulcer cases. In his recent work, Rosenow<sup>4</sup> has pointed out new methods of studying ulcer cases which we have applied not only to our present series of cases, but also to great advantage to those cases described by one of us six years ago.

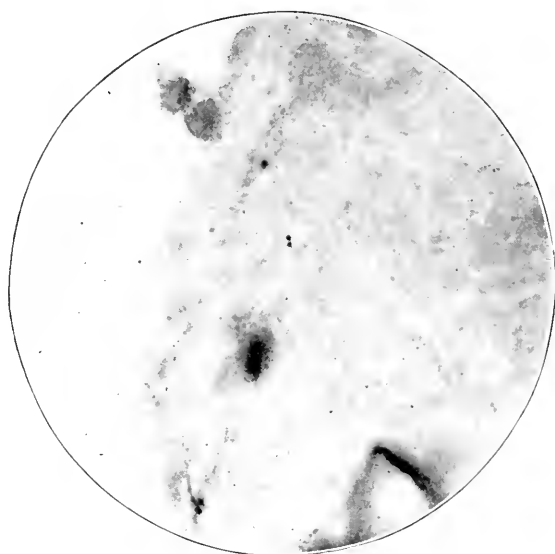


Fig. 1.—Photomicrograph of section from Case 1.

The following is a brief statement of the eleven ulcer cases, including clinical history, necropsy, and microscopic findings, as well as the examination for bacteria. The cases in which cultures were made from the ulcers at necropsy are also indicated. All the cases were observed between Sept. 24, 1914, and April 14, 1915.

#### REPORT OF CASES

CASE 1.—W. H. B., a male infant 3 months of age, was admitted to the hospital Oct. 21, 1914. The birth was normal. He was breast fed three weeks and then bottle fed at irregular intervals. He was never very well after he was 3 weeks old. The present illness was of about three weeks' duration;

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4. Rosenow, E. C.: Bacteriology of Ulcer of the Stomach and Duodenum in Man, *Jour. Infect. Dis.*, 1915, xvii, 219.

diarrhea and vomiting. One week before admission he was given boiled skimmed milk and water,  $1\frac{1}{2}$  ounces of each, every three hours. For a few days he improved. On the day of admission he passed blood in large amounts from the bowels. On admission the patient was in a state of collapse. He continued to pass a large quantity of dark blood from the bowels and died in less than twelve hours, Oct. 22, 1914.

*Necropsy.*—The body is that of a markedly emaciated male baby. The stomach is slightly thickened; no ulceration. On opening the peritoneal cavity there is seen a circumscribed peritonitis about the duodenum. The duodenum just beyond the pyloric ring shows a submucous hemorrhage measuring about  $\frac{1}{2}$  cm. in diameter. Just beyond the hemorrhage is a region of induration involving the duodenum on posterior and outer portion of first curvature and extending about three-quarters around the duodenum. In the center of the region of induration is seen a clear cut perforation of the wall measuring  $\frac{3}{4}$  by  $\frac{1}{4}$  cm. and running parallel to the duodenum. The ulcer measures  $2\frac{1}{2}$  by  $1\frac{1}{2}$  cm. The base of the ulcer is smooth, white, and is covered with black clots of blood. At its lower end is a lateral extension measuring  $\frac{1}{2}$  by  $\frac{3}{10}$  cm. There is dark tarry blood throughout the entire intestinal canal.

*Anatomic Diagnosis.*—Perforated duodenal ulcer, melena, encapsulated peritonitis.

*Microscopic Examination.*—Section stained with hematoxylin and eosin: The ulcer is rather shallow for about two-thirds of its extent and then dips down involving the circular muscular layer. In this area a large vessel is completely surrounded by necrotic tissue; its wall, however, is still intact. In the shallow portion of the ulcer there is a very wide zone of necrosis in which all structure is lost. The ulcer is characterized by more infiltration than is usually seen in the deeper layers of the duodenum.

Section stained for bacteria by the Gram-Weigert method: The section shows very beautifully several pairs of diplococci and numerous other cocci in the tissue below the surface of the ulcer in its deepest portion. Figure 1 is a photomicrograph taken from this section.

The following three cases are of particular interest because of the association with tuberculosis. In our previous series there was one case of tuberculosis that had numerous acute duodenal ulcers. We wish to separate these three cases from the remainder, however, because two were in older children and because the anatomic specimens were lost and there is a remote possibility that these ulcers were of tuberculous origin.

CASE 2.—S. F., a female child 10 years of age was admitted to the hospital Dec. 12, 1914. She had been a normal, healthy child. Had scarlet fever, chicken-pox and measles about 3 years before. The present illness was of about two weeks' duration. It began with sharp basal headache, high constant fever, malaise, anorexia, epistaxis and constipation. There had been a single attack of vomiting, profuse sweating and increasing apathy.

*Examination.*—Examination on admission showed a well developed, well nourished girl of 10 years, apathetic and slow to answer questions. The pupils were unequal; react to light; the eyegrounds showed evidence of increased intracranial pressure. The neck was held slightly rigid; there was some rigidity of extremities; the reflexes were active. The condition became slowly worse from day to day, until death Dec. 20, 1914.

*Clinical Diagnosis.*—Tuberculous meningitis.

*Necropsy.*—The body was that of an emaciated girl. The right lung contains numerous areas of bronchopneumonia. The bronchial lymph glands showed no tuberculous process. There was fatty degeneration of the liver. The stomach was negative. The duodenum as well as the ileum and the jejunum contained much bloody, tarry material. The duodenum contained a number of ulcers from pinhead to split-pea size.

*Anatomic Diagnosis.*—Tuberculous meningitis. Bronchopneumonia. Duodenal ulcers. Melena.

CASE 3.—A. J., a female child 2 years of age, was admitted to the hospital Jan. 2, 1915. Her father had pulmonary tuberculosis but "was cured." Birth was normal; her weight was 8 pounds. She was breast fed once each day and received cow's milk every four hours. When two weeks old she had convulsions, and five months before admission had bronchopneumonia. Since she was 6 months old had a discharging ear.

Duration of present illness, five days. She was fretful; coughed, vomited once and had fever. She appeared stupid. She had two or three stools daily, yellowish green and slimy.

*Examination.*—The examination on admission showed a dull, rather well nourished child, with cough, labored breathing, discharging left ear, carious teeth and enlarged, red tonsils. The lungs showed slight, not well defined dullness at right apex and axilla; moist râles over the entire chest. On the left side there were large mucous râles, over the upper right front and axilla and lower back, coarse râles; over the right posterior upper lobe there were subcrepitant râles and bronchial breathing. The stools were soft and yellow. No vomiting.

Death occurred Jan. 4, 1915.

*Clinical Diagnosis.*—Miliary tuberculosis.

*Necropsy.*—Well nourished girl. There are miliary tubercles in liver and spleen. An old fibroid nodule is seen in upper lobe of right lung. Right and left lower lobes are infiltrated. There are many typical undermined tuberculous ulcers opposite the mesentery in the ileum. Large healed tuberculous lymph gland at the beginning of jejunum. The duodenum is markedly reddened and shows several ulcers.

*Anatomic Diagnosis.*—Primary tuberculosis of upper lobe of right lung. Tuberculous lymph adenitis. Acute bronchopneumonia. Miliary tubercles of lungs, liver and spleen. Multiple tuberculous ulcers of small intestine. Multiple ulcers of duodenum.

CASE 4.—H. S., a female child 2½ years of age, was admitted to the hospital Jan. 7, 1915. Previous health had been good. Present illness was of two months' duration. Onset was with pains in back and right knee, nervous twitchings, cough and constipation.

*Examination.*—Examination on admission showed a well nourished child. Lungs: There was dullness at right apex front and back and slight impairment of note on left. Fine crackling râles were heard over the area of dullness. The extremities showed slight spasticity. Kernig's, Babinski's and Brudzinski's signs were positive. (The spinal fluid injected into a guinea-pig produced miliary tuberculosis.)

The condition grew worse and the patient died Jan. 12, 1915.

*Clinical Diagnosis.*—Miliary tuberculosis; tuberculous meningitis.

*Necropsy.*—Well nourished girl. The brain showed excess of fluid; the meninges were studded with small yellowish gray tubercles. A primary tuberculous lesion was found in upper lobe of right lung. There were miliary tubercles in spleen and liver. Duodenum was markedly reddened and its first portion contained numerous ulcers. Duodenum contained much blood.

*Anatomic Diagnosis.*—Primary tuberculosis of upper lobe of right lung. Tuberculous broncholympadenitis. Miliary tuberculosis of spleen, liver and brain. Duodenal ulcers.

CASE 5.—A. S., a male infant 1 month of age, was admitted to the hospital Jan. 15, 1915. Birth normal, weight 9½ pounds. He was never breast fed. He was given condensed milk at first and later cow's milk. The present illness was of two weeks' duration; manifest loss of weight, coryza.

*Examination.*—Examination on admission showed an exceedingly emaciated, cyanotic, poorly cared for infant. There were excoriations of buttock and genital regions, and an ulcer on right foot. The stools passed contained a large mass of dark clotted blood. The infant died eight hours after entering the hospital.

*Necropsy.*—The body is that of a markedly emaciated male infant. Stomach contains mucus with brownish flecks. Duodenum: The surface is reddish and there is a slight amount of blood in the lumen. There are several ulcers of the peptic type, one the size of a split pea, the others pinhead in size.

*Anatomic Diagnosis.*—Atrophy. Multiple ulcers of duodenum.

*Microscopic.*—Section stained with hematoxylin and eosin. The section is of an ulcer overlying the pancreas, including a small portion of mucous membrane. The ulceration has extended completely through the duodenal wall and the greater portion of the base of the ulcer is formed by the pancreas. The portion of the mucosa seen in the section contains an excessive amount of connective tissue, in which lie large numbers of eosinophils. The remains of the muscular coats are only very slightly infiltrated with lymphoid cells, occasional small clumps are seen. The base of the ulcer over the pancreas consists of a necrotic zone of pancreatic tissue with practically no cellular infiltration. The eosinophils are present in excessive numbers in the connective tissue, although not as marked as in the mucosa.

Section stained for bacteria by the Gram-Weigert method. In the portion of the ulcer base consisting of partially necrotic gland tissue are a few pairs of diplococci. In the muscular part of the ulcer base nothing was found.

CASE 6.—B. L., a male infant, 3 months old, was admitted to the hospital Dec. 27, 1914. Present illness of three days' duration; fever and cough.

*Examination.*—Examination on admission showed a poorly developed, poorly nourished infant. Stools very loose, green and mucous; about four each day. He was started on a weak milk mixture and later given whey modified milk (Schloss). The stools continued loose and frequent, green and mucous throughout his entire stay in the hospital. Jan. 23, 1915, the stools contained dark and fresh blood. Death occurred early the following morning, January 24.

*Necropsy.*—The intestines are distended and of a bluish-green hue. Stomach normal. Duodenum: near the papilla is an ulcer measuring 5 mm. in diameter. The edges are smooth and the base is irregular and dark. There are several small pinhead sized ulcers in the first part of the duodenum. Ileum and colon are filled with black tarry fecal material.

*Anatomic Diagnosis.*—Atrophy. Duodenal ulcers. Melena.

*Microscopic.*—Section stained with hematoxylin and eosin. The section is taken through the base of the ulcer overlying the pancreas. No portion of the normal mucous membrane is present, only the wall of the ulcer involving the submucosa, muscular coats and pancreatic tissue. The base of the ulcer involving the duodenum is in part densely infiltrated with lymphocytes, in part practically free from cells. The connective tissue is, in part, of the young endothelial type, especially about a large blood vessel running parallel to the surface of the ulcer. In several places there are small areas of necrosis with fragmentation of the nuclei. In the pancreatic tissue there is a zone of demarcation between the surface of the ulcer and the normal pancreatic tissue in which there is a

coarse network of material which stains deeply with hematoxylin. Eosinophil cells are present in moderate numbers, especially about the vessels.

Section stained for bacteria by the Gram-Weigert method. The section shows only very few scattered diplococci in the base of the ulcer, in about the middle of the base and also slightly toward one side. None are to be found in the submucosa at either side of the ulcer.

CASE 7.—M. McB., a female infant, aged 5 months, was admitted to the hospital Jan. 29, 1915. The birth was normal, one of twins, weight 7 pounds, 6 ounces. Breast fed four weeks, supplemented by a cow's milk mixture. Then equal parts of cow's milk and water. The present illness was of indefinite duration. There had been gradual loss of weight.

*Examination.*—Examination on admission showed a poorly nourished infant with increased rate of respiration. Profuse discharge from nose and from both ears. The head was slightly retracted but no rigidity of neck. Chest: many medium and fine moist râles were heard over right back. Extremities were somewhat rigid.

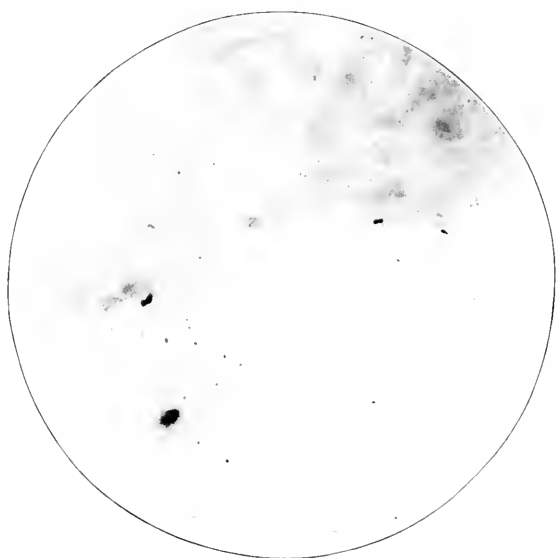


Fig. 2.—Photomicrograph of section from Case 7.

February 12, patient had a convulsion. Examination shortly afterward showed patient cyanotic, respiration shallow. Fontanel tense and slightly bulging. Right pupil was larger than left. There was no rigidity of neck. Chest: there was dulness over right back and front. High pitched medium and fine râles and tubular breathing. Lumbar puncture—cloudy fluid—and smears showed gram-negative bacilli.

Following a convulsion in the evening the patient vomited a small amount of "coffee ground" material which gave a positive test for blood.

The patient died the next morning, Feb. 13, 1915.

*Clinical Diagnosis.*—Influenzal meningitis and duodenal ulcer.

*Necropsy.*—No free fluid in the abdominal cavity. Intestines distended, of a bluish-gray color. Lungs: small area of consolidation in right upper lobe. Right ureter enlarged and swollen. Hemorrhage in left adrenal. Stomach negative. Duodenum: in the first one-third of the duodenum is an ulcer about  $\frac{1}{2}$  cm. in diameter with smooth and regular edges. No evidence of recent

hemorrhage. About  $\frac{1}{2}$  cm. below is another smaller ulcer. Small intestine and colon filled with tarry material.

The brain was covered with a thick, creamy exudate. Brain substance was soft and hyperemic.

*Anatomic Diagnosis.*—Purulent meningitis. Encephalitis. Duodenal ulcer, melena. Bronchpneumonia. Fatty degeneration of parenchymatous organs.

*Microscopic.*—Section stained with hematoxylin and eosin. The section of this ulcer is one of the most interesting of the series; it is the ulcer from which a *Streptococcus viridans* was cultivated which on injection into animals produced gastric and duodenal ulcers. This will be reported in detail by one of us at a later date. The ulcer is of further interest in that it shows a large vessel in its base just about ready to rupture. The tissues are well preserved, the mucous membrane to the side of the ulcer is practically intact; at the edge of the ulcer, the glands of Lieberkuhn show some proliferation and tendency to form stellate cells in masses. The submucosa in the ulcer base is markedly edematous. This edema gradually subsides toward the normal tissue. The very edge is densely infiltrated with leukocytes. Where the inner muscular layer forms the base of the ulcer it is also edematous, especially so about the large vessel mentioned above, where it extends through to the serosa. The serosa is rather edematous in its entire extent under the ulcer. The wall of the vessel in the serosa is practically normal, the cells stain well and have a chromatin network; as it approaches the surface, however, there are no nuclei to be made out. A small lymph gland attached to the section shows considerable proliferation of the epithelioid cells in its germ centers.

Section stained for bacteria by the Gram-Weigert method: This section of the ulcer shows numerous diplococci in the base of the ulcer and in the side of the ulcer. At the level of the submucosa a short distance below the surface are a group of four pairs of diplococci, and scattered through the tissue adjacent there are other groups of diplococci. Figure 2 is a photomicrograph of this ulcer.

CASE 8.—R. R., a male infant 6 months of age, was admitted to the hospital Feb. 23, 1915. His birth was normal. He was breast fed only two months. The present illness began four days before admission, with convulsions, a bloody diarrhea, vomiting and high fever.

*Examination.*—Examination on admission showed a well nourished baby, quite ill, skin doughy, respiration rapid. There were a few fine râles over the chest. The abdomen was held rather rigidly, especially the right side where there was marked tenderness. No mass was palpable. Dark stools were passed.

Laparotomy was performed. The large intestines were greatly injected. Appendix was swollen, hyperemic, and the follicles prominent. The removed appendix showed no perforation. There was no intussusception. The dark contents of the ileum suggested blood. The patient vomited "coffee ground material." The death of the patient occurred about four hours after the operation, Feb. 23, 1915.

*Necropsy.*—The liver is large, firm and yellow, its section very fatty; the spleen pulpy and red and the kidneys swollen and yellow. The stomach contains a small amount of brown sticky mucus, but no ulcers. Duodenum: there is a large ulcer about 5 mm. in diameter. The surface of the duodenum is red and swollen. The colon shows many superficial ulcerations.

*Anatomic Diagnosis.*—Ulcer of the duodenum. Colitis. Fatty degeneration of parenchymatous organs. Acute splenic tumor.

Cultures made from ulcer base, at necropsy, were completely overgrown by colon bacilli, though some streptococci were present in the smears made from the original culture.

*Microscopic.*—Section stained with hematoxylin and eosin. The section is through one side and a portion of the base of the ulcer. There is relatively

little infiltration in the base and margin of the ulcer. There is a gradual slope from the margin to the bottom of the ulcer which in its middle position is made up of necrotic muscularis. Several large vessels in the submucosa near the surface of the ulcer show no evidence of thrombosis. The serosa is not infiltrated.

Section stained for bacteria by the Gram-Weigert method: The section shows very numerous streptococci throughout the entire base of the ulcer, at the surface as well as deep down in the tissue.

CASE 9.—J. M., a female infant 3 months of age, was admitted to the hospital March 18, 1915. The birth weight was  $7\frac{1}{2}$  pounds. She was never breast fed. The stools were always thin and greenish. The present illness was of four days' duration. The baby seemed ill. Examination on admission showed an extremely emaciated, small, weak baby. Respirations were shallow. There was impaired resonance over upper right front and back, medium râles were present over right back, a few over left. Abdomen scaphoid. Liver and spleen slightly enlarged. Death about eight hours after admission.

*Necropsy.*—The right upper lobe, paravertebral regions of both lower lobes are consolidated. The liver is very hyperemic. Stomach: Pyloric half of stomach is studded with numerous pinhead sized punched out ulcers. The same small pinhead sized ulcers are seen in the first part of the duodenum. The culture taken from the ulcer at necropsy showed only colon bacilli.

*Anatomic Diagnosis.*—Bronchopneumonia. Multiple ulcers of stomach and duodenum.

*Microscopic.*—Section stained with hematoxylin and eosin: The section shows the mucosa on either side of a small ulcer, which extends down to, but does not involve, the muscular layer. On one side the ulcer dips abruptly down, on the other side it slopes down gradually. The side of the ulcer, and to a lesser extent the base of the ulcer, are densely infiltrated with cells. The usual necrotic zone in the base is not evident. The Lieberkühn glands show no change.

Section stained for bacteria by the Gram-Weigert method. Streptococci were looked for in four sections. In only one were they found. Most typical was a pair of streptococci deep in the ulcer wall in the area of the submucosa. No other bacteria were found in the section.

CASE 10.—Charles P., a male infant 6 months of age, was admitted to the hospital April 14, 1915. The birth was normal. He was breast fed only three days, then given condensed milk. For two months before admission the baby had cried much, vomited after every feeding and was always constipated. Examination showed a small, poorly-nourished baby with shallow respirations. Loose, yellow, mucous stools. Death occurred on the evening of admission, April 14, 1915.

*Necropsy.*—Duodenum: There is an ulcer about 1 cm. from the pylorus, elliptical in shape, with blackened margins and roughened base, measuring  $\frac{3}{4}$  by  $\frac{1}{2}$  cm. The remainder of the duodenum is very red, also the first part of the jejunum. The cultures from the ulcer base were overgrown with colon bacilli.

*Anatomic Diagnosis.*—Atrophy. Duodenal ulcer. Melena.

*Microscopic.*—Section stained with hematoxylin and eosin: The section shows an ulcer of moderate size, extending down into the submucosa. There is marked infiltration of the base as well as of the sides of the ulcers. One side of the ulcer is abrupt; the other side slopes gradually down from the normal mucosa. The muscular layers show no infiltration.

Section stained for bacteria by the Gram-Weigert method: In the base of the ulcer just below the surface there is a pair of streptococci. No other bacteria to be seen in the section.



CASE 11.—A. S., a male infant 2 months of age, was admitted Aug. 9, 1914. His birth weight was 7 pounds. He was being fed cow's milk, one-third dilution. For two days he had fever and diarrhea; green stools every hour, but no blood. There was no vomiting. Examination on admission showed a small fairly well nourished infant. There was a fine papulovesicular rash over the entire body. Abdominal walls were normally resistant. Liver was slightly enlarged. There was a trace of albumin and a few leukocytes in the urine. The stools were frequent, green and mucous. The infant was given albumin milk. For a short time there was a little improvement, but stools were rather frequent, green and mucous and there was some regurgitation. September 16 there was a sudden rise of temperature to 103 F. It then dropped below normal. Stools began to show traces of blood. Patient vomited bright red blood and later "coffee ground" material. No bleeding points in mouth or pharynx.

The next day, September 17, patient appeared in better condition. There was no more regurgitation of food or blood. Stools gave positive chemical test for blood.

September 19, patient appeared paler, had no rigidity of abdomen, but edema of dorsal surface of hands and feet. September 21 there was edema of face and head; also there was regurgitation of food, but no blood. Abdomen was rather tense. Fulness in gastric area was marked but no peristaltic waves were seen. September 22 there was general edema, dyspnea and continuous regurgitation. Death Sept. 24, 1914.

*Clinical Diagnosis.*—Gastro-enteritis. Duodenal ulcer. Acute nephritis.

*Necropsy.*—Moderate state of nutrition. The kidney cortex is red and swollen. Stomach is markedly reddened, no ulceration. In the first portion of duodenum there is a small punched out area with small central scar.

*Anatomic Diagnosis.*—Acute nephritis. Healed duodenal ulcer.

*Microscopic.*—Section stained with hematoxylin and eosin: The block was taken through the middle of the little depression which is all that is to be seen of the ulcer at the necropsy. The section shows a swelling instead of a depression in its middle portion. This swelling is due to a very marked infiltration with small round cells, of all of the coats of the duodenal wall. The mucosa lining over the swollen portion is not intact. The most marked infiltration is in the layer of the Lieberkühn glands. The glands are forced wide apart by the lymphocytic infiltration. The inner muscular layer is so separated by the infiltration that it is difficult to make it out distinctly. The outer muscular coat is also densely infiltrated, and along the vessels passing through there is a marked collection of cells. The serosa is infiltrated for a considerable distance beyond the thickened area.

Section stained for bacteria by the Gram-Weigert method: In the middle of the thickened area where the mucosa and submucosa are markedly infiltrated, there are numerous diplococci lying in the tissues a short distance below the surface. In this same area there are several chains of four members.

Before passing on to a discussion of these cases, it seems advisable to give in detail the results of an examination of all the ulcers still available for microscopic study of Series I and II previously reported by one of us.<sup>1, 5</sup> In order not to take up too much space the ulcers have been numbered, and with each one the case number and name as well as the series is given, so that they can be identified in the previous communications.<sup>1, 5</sup>

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5. Helmholtz, H. F.: Duodenal Ulcer in Infancy, Arch. Pediat., 1909, xxvi, 661.

The sixteen cases reported were practically all cases of atrophy, with single or multiple duodenal ulcers. Of the sixteen cases described there were 14 ulcers from 11 different cases available for study. No blocks of tissue were available, only sections stained with hematoxylin and eosin. In some instances only a single section was at hand. The sections were decolorized with acid alcohol and were stained by the Gram-Weigert method.

The findings in the ulcers were as follows:

ULCER 1 (Case 1, Series I, Ernest M.).—Section of the ulcer shows numerous streptococci in tissue just beneath ulcer surface. The cocci are arranged in a row parallel to the surface in four groups of twos.

ULCER 2 (Case 2, Series I, Hildegard O.).—After prolonged search it was impossible to find any streptococci. Two sections were available.

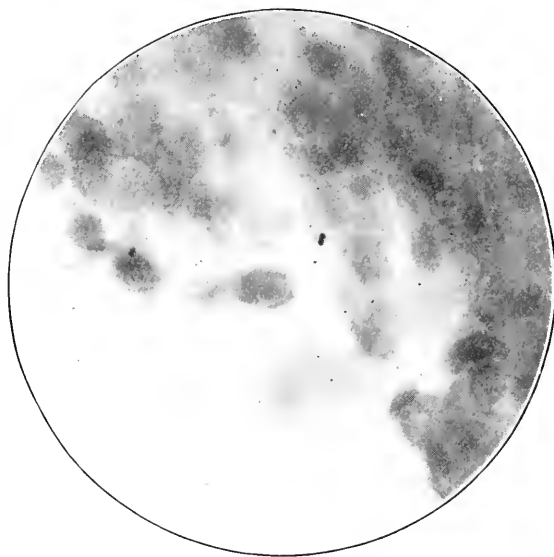


Fig. 3.—Photomicrograph of section in Case 8, Series I, Timm M., Ulcer 8.

ULCER 3 (Case 4, Series I, Willie R.).—Only single partially healed ulcer was available, repeated prolonged search failed to reveal any streptococci.

ULCER 4 (Case 5, Series I, Kurt Kruggel).—The section is of an ulcer that perforated the duodenal wall. In the portion of the ulcer where the base is formed by the inner muscular coat there is seen just below the surface of the ulcer a pair of streptococci somewhat larger than usual. No other bacteria were found in the entire section.

ULCER 5 (Case 6, Series I, Alfred K.).—Two sections of an ulcer that differs from the others in that it shows very much more leukocytic infiltration than any of the other ulcers. Repeated prolonged search did not reveal any bacteria.

ULCER 6 (Case 7, Series I, Erich S.).—Two sections of the ulcer were at hand. Careful search on several occasions revealed no bacteria whatsoever in the sections.

ULCER 7 (Case 8, Series I, Timm M.).—A small ulcer extends down into the muscular coat with the remains of a small clot in the ulcer base. In the base of the ulcer just beneath the surface, where it is made up of the muscular layer, there are three pairs of diplococci.

ULCER 8 (Case 8, Series I, Timm M.).—Section is through the wall of an ulcer that has completely eroded the duodenal wall. In the wall consisting of submucosa there are three distinct pairs of diplococci to be seen just below the surface of the ulcer. No bacteria were found elsewhere in the section. A pair of the cocci are shown in Figure 3.

ULCER 9 (Case 4, Series II, H. Ulrich).—Ulcer is a rather superficial one in which only a portion of the ulcer extends deeply down into the muscular coat. On the surface towards one side lying deep in the tissue are two groups of diplococci. The rest of the section shows no bacteria.

ULCER 10 (Case 4, Series II, H. Ulrich).—The ulcer is partially healed, epithelium growing in from the side. In almost the middle of the ulcer, just

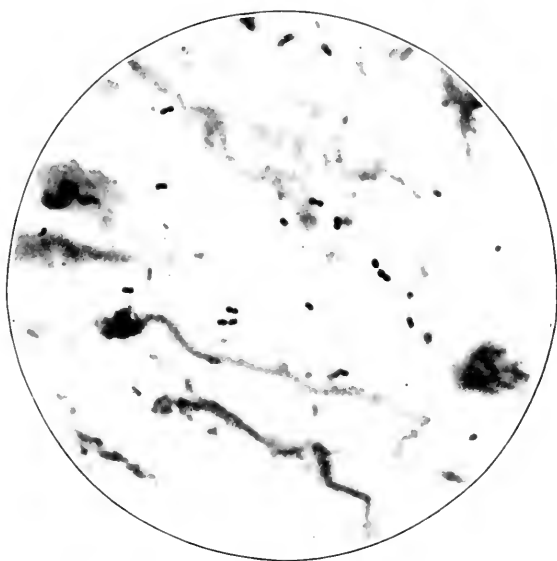


Fig. 4.—Photomicrograph of Ulcer 12, Case 5, Series II, Alf. Gerlach.

below surface, there is a group of four pairs of diplococci and at a short distance another pair of diplococci.

ULCER 11 (Case 4, Series II, H. Ulrich).—Sections contain two ulcers. In base of the larger one, are seen numerous cocci lying in the tissue just beneath the surface of the ulcer. The cocci are in short chains and pairs.

ULCER 12 (Case 5, Series II, Alf. Gerlach).—This ulcer is interesting because of the fact that it has absolutely no inflammatory reaction about it and is the type of ulcer that is usually considered an erosion rather than a definite ulcer. This ulcer is of all the ulcers the one in which the streptococci were most numerous. Practically the entire base of the ulcer, made up of submucosa, is studded with diplococci and streptococci in short chains. This portion of the section is shown in Figure 4.

ULCER 13 (Case 5, Series II, Alf. Gerlach).—Another section of the above case contains two ulcers both of which show in their base and sides numerous diplococci and streptococci.

ULCER 14 (Case 6, Series II, K. Lieback).—Stained with hematoxylin and eosin. The section could not be restained because of a broken slide. The ulcer shows, however, in the portion of the base consisting of submucosa, a single pair of streptococci of very definite outline.

#### SUMMARY

In ten out of fourteen ulcers from the two previously reported series, in which only one or two sections of each were available for study, diplococci were found in the ulcer base, and in all eight ulcers of our present series diplococci were found in the ulcer in such numbers and in such a position that they presumably are of etiologic significance. Furthermore, in one of the cases a *Streptococcus viridans* was isolated from the duodenal ulcer, which on injection into rabbits and dogs localized in the pyloric end of the stomach and duodenum and there produced hemorrhages and ulcerations. This case was the only one in which we were able to obtain the organisms in pure culture, and the only one in which the necropsy was performed shortly after death. In two other cases a few streptococci were seen in the bouillon cultures, but the cultures were so overgrown with colon bacilli that it was impossible to isolate the streptococci. In the fourth case only the colon bacillus was grown.

Rosenow<sup>4</sup> has recently shown that from duodenal and gastric ulcers removed at operation, a streptococcus viridans can be constantly isolated, which when injected intravenously into dogs and rabbits will tend to localize in the stomach and duodenum and there produce first hemorrhage and later ulcers. In explanation of this phenomenon he assumes that the streptococcus producing duodenal ulcer finds in the duodenum conditions peculiarly favorable for its development, and therefore tends to localize there when injected intravenously into animals. Whether this tendency to localize is a question of oxygen tension or of some other factor does not interest us at the present time; only the fact that there is a streptococcus which shows this peculiar predilection for the duodenal mucosa. In other words, we can assume that at times, because of circumstances at present not well understood, the streptococcus takes on characteristics which make it tend to localize in the duodenum when infecting an infant. We have thus a working hypothesis which explains very readily the epidemic appearance of duodenal ulcers; namely, that we have an infection with a very definite organism, which, carried to the infant either through the digestive tract or through the air passages, tends to localize in the duodenum. This same tendency to localize in specific tissue has been shown by Rosenow to be true of the streptococcus isolated from cases of rheumatic fever, endocarditis, appendicitis and herpes zoster, when injected into animals. Not only is the organism specific when isolated

from the characteristic lesion, but usually when isolated from the portal of entry, such as the tonsils, an alveolar abscess, etc. Rosenow has quite conclusively established the fact that gastric and duodenal ulcer of the adult are the result of an infection with a streptococcus of particular virulence. That this holds good for duodenal ulcers of the infant also is very definitely shown by the following facts summarizing our work:

1. The appearance of duodenal ulcer in epidemic form.
2. The presence of diplococci and streptococci in all the ulcers of our present series available for study, and in ten out of fourteen ulcers of a previous series of cases.
3. The isolation, at necropsy, from one ulcer, of a *Streptococcus viridans* which when injected into dogs and rabbits localized in the pyloric end of the stomach and the duodenum and produced there hemorrhages and ulcers.

Regarding the symptomatology of duodenal ulcer we have nothing to add, it being practically never possible to diagnose the condition until there are complications from the ulcerative process, such as rupture of a vessel, or perforation into the peritoneal cavity.

Death occurred within forty-eight hours in all cases of hemorrhage, excepting one in which death occurred after one week from an intercurrent infection; the ulcer was practically healed, showing how rapid the healing is even in infants who are markedly atrophic. Occurring as a complication usually in atrophic infants, the prognosis is always bad. Transfusion as described by one of us<sup>6</sup> might be of some value if performed immediately.

In conclusion we wish to thank Dr. Rosenow for his kind suggestions and his assistance in this work.

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6. Helmholz, H. F.: The Longitudinal Sinuses as a Place of Preference for Transfusion in Infancy, AM. JOUR. DIS. CHILD., 1915, x, 147.

## A COMFORTABLE ARRANGEMENT FOR THE SEPARATE COLLECTION OF URINE AND FECES OF MALE INFANTS \*

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Of the utmost importance in the quantitative investigation of infant excretions is the absolutely complete collection of the separate urine and feces for the desired period. Hardly second in importance is the question of comfort for the child, for it is possible that a constrained or unusual posture appreciably affects the metabolism. For example, one arrangement, in which the body is partly supported as in a hammock, brings considerable pressure on the lower part of the back and in some cases has seemed to cause increased peristalsis. With another method the bed is necessarily slightly tilted and the child held from slipping by an elaborate system of straps so arranged as not to press on any part of the body but holding shoulders and arms in an almost immovable position.

The arrangement here described is recommended as combining accuracy of collection with a maximum of comfort for the child. It is mainly a satisfactory combination of details from methods in use. The Finkelstein<sup>1</sup> rubber and glass contrivance, which experience in the Babies' Hospital has shown to be the most accurate for collecting urine, is somewhat modified to suit an entirely different arrangement for supporting the child. The means used to hold the child from slipping, although adopted independently here, is practically the same as that employed in Talbot's<sup>2</sup> metabolism bed. An air cushion is used in Schabad's<sup>3</sup> scheme, but so far as is known no use has elsewhere been made of the air cushion with an opening in the rim. This method can be carried out on any crib or bed by making the necessary modifications of the mattresses. It is more convenient to use an adjustable crib in which the bottom can be raised to bring the child to a convenient level for handling.

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\* Submitted for publication Aug. 20, 1915.

\* From the Laboratories of the Rockefeller Institute for Medical Research and the Babies' Hospital.

\* Thanks are due to Dr. E. A. Morgan, Resident Physician of the Babies' Hospital, for taking photographs.

1. Bendix and Finkelstein: *Deutsche med. Wchnschr.*, 1900, xlii, 672.

2. Talbot, F. B.: *Apparatus for Metabolism Experiments in Male Infants*, *Jour. Am. Med. Assn.*, Nov. 27, 1908, p. 1818.

3. Schabad: *Arch. f. Kinderh.*, 1908, xlviii, 402.

The following articles are required:

1. Mattresses, all of the ordinary thickness. One piece (*A*) 20 x 23 inches; two pieces (*B*) 6 x 8 inches; two pieces (*C*) 8 x 16 inches, for a crib 21 x 48 inches.
2. Rubber air cushion. Outside diameter 12 inches; inside diameter 3½ inches. Opening when inflated about 2 inches.
3. Cloth cover for cushion, consisting of two 18-inch squares with a circle 3½ inches in diameter cut out of the center, the pieces being stitched together around the circle and free on all sides.

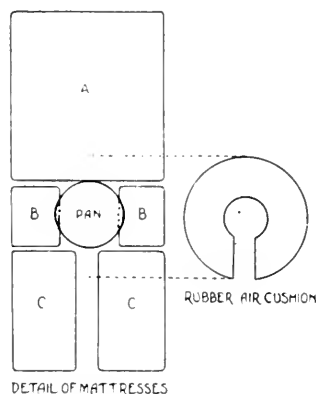


Fig. 1.—Diagram showing detail of mattress and rubber air cushion.

4. Enamel ware pan with flange, 9 inches in diameter.
5. Ordinary male glass urinal.
6. Finkelstein rubber attachment.
7. Glass tube (after Finkelstein, but lighter and differently bent).
8. Cloth strap made of two pieces of webbing, each 6 inches wide, one 28 inches long, placed on the other which is 36 inches long, and the two stitched together across the middle.

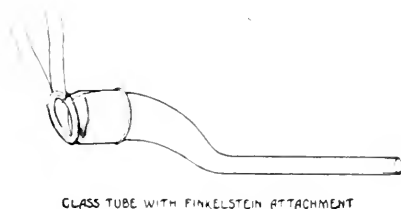


Fig. 2.—Drawing of glass tube with Finkelstein attachment.

Directions for setting up:

Cover mattresses separately with sheets, pinning on under side. Place mattresses and pan in position according to diagram Figure 1. It is convenient to lay a circle of oiled silk in the bottom of the pan.

Inflate rubber cushion not too hard, place within cloth cover, and pin down snugly on mattresses, with opening toward bottom of bed.



Fig. 3.—Material of metabolism bed assembled.

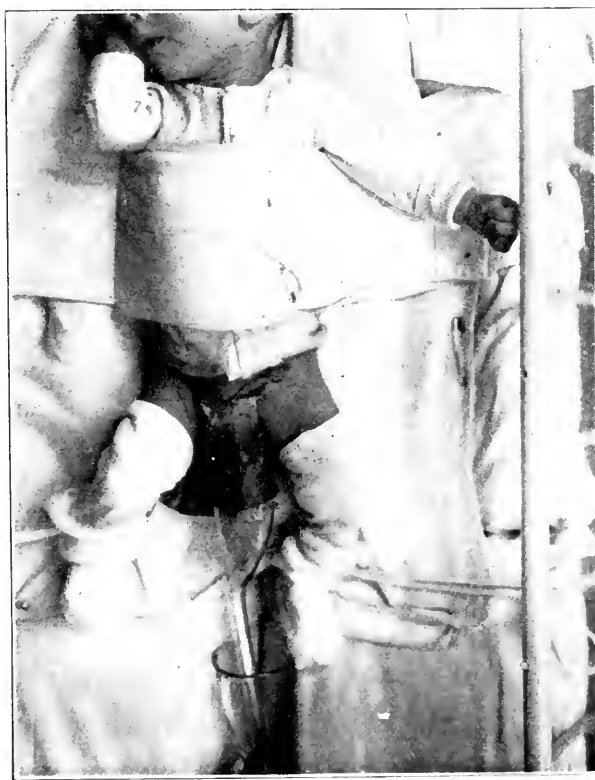


Fig. 4.—Infant in the metabolism bed with apparatus applied.



Place cloth band across mattress A with lower edge just above lower edge of mattress and pin ends of bottom strap tightly to sides of mattress.

Place child on bed with anus directly over hole in rubber cushion, buttocks resting comfortably on cushion. If necessary, lay a pad under back above where he rests on the cushion.

Insert the large end of the glass tube (Fig. 2) in the end of the rubber attachment, pushing it in well.

Place small end of glass tube in neck of urinal and make the latter secure between cushions C.

Attach the rubber to the child, putting scrotum and penis within the large end of the glass tube and bring the rubber close to the body. Draw the rubber straps around the body, crossing on the back and fasten ends together in front with adhesive plaster. Make secure but not tight. Place absorbent cotton under rubber wherever it seems advisable.

Pin the ends of the upper strap of the cloth band snugly around the body.

The infant's legs rest on cushions C.

Ankles should be tied loosely by wide tapes, with absorbent cotton under the tape, to the sides of the crib, allowing some movement of the legs but not enough to cause disturbance of the urinal.

The glass tube in the rubber attachment resting in the space between the ends of the air cushion gives sufficient drop to assure the flow of the urine into the urinal.

Cushion B can easily be removed to facilitate changing the enamel pan.

A thin board between springs and mattresses will prevent any air currents from reaching the child from beneath.

With a very small or very restless child frequent inspection at the beginning is advisable to make sure that the rubber adjustment has not slipped, but ordinarily the necessary visits at intervals to remove the samples of urine and feces to the icebox are sufficient to make sure that all is right.

## OXALIC ACID EXCRETION IN THE URINE OF CHILDREN \*

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So far as I have been able to find, there are but two references in pediatric literature to the determination of the oxalic acid content of the urine of infants. The first is in the handbook of Pfaundler and Schlossmann<sup>1</sup> published in 1906, and is as follows: "The studies of Sedgwick at the Heubner Clinic have shown us that children excrete absolutely larger amounts of oxalic acid than adults."

The second reference appeared last year in an article by Hans Aaron and Marianne Franz,<sup>2</sup> on the "Organic Acids in the Urine of Infants." They state that, so far as they know, no examinations of infants' urines for oxalic acid appear in the literature. They mention records in the literature of the finding of 9 to 11 mg. of oxalic acid in the day's urine of a dog during the second week of starvation, and state that this must be endogenous oxalic acid. In addition to this, it is known that oxalic acid may be formed in the intestine as a byproduct of carbohydrate fermentation. From these facts and other studies on adults, it is generally accepted that there may be an endogenous formation of oxalic acid in the human metabolism, even on an oxalic acid free diet. It is also recognized, from examinations of the urine of rabbits, that a carbohydrate diet may increase the excretion of oxalic acid in the urine. This is supposed to be due to the imperfect oxidation of the glycuronic acid produced and a secondary formation of oxalic acid.

Hildebrandt<sup>3</sup> gave rabbits that were being fed oats 30 gm. of glucose per day. These animals died with symptoms of acute intoxication. However, when he gave such animals lime with the same amount of sugar, they bore the diet without inconvenience. He explained this protective action of calcium by the supposition that the oxalic acid formed was bound by the calcium and rendered non-toxic. The work of Aron and Franz led to the following conclusions:

1. The urine of infants contains small amounts of oxalic acid almost without exception. It is found even when they are on oxalic acid free diets, such

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\* Submitted for publication Sept. 6, 1915.

1. Pfaundler and Schlossmann: *Handbuch der Kinderheilkunde*, 1906, ii, 522.

2. Aaron and Franz: *Organic Acids in the Urine of Infants*, *Monatschr. f. Kinderh.*, 1914, xii, O., p. 645.

3. Hildebrandt, H.: *Ztschr. f. physiol. Chem.*, xxxv, 141.

as breast milk or cow's milk and sugar, and this must be considered as either from the intestine, as a byproduct of carbohydrate fermentation or formed in the intermediary metabolism, that is, endogenous oxalic acid formation.

2. After feeding of cane sugar or dextrin-maltose preparations, the oxalic acid excretion was somewhat higher than on an exclusively milk diet. Starchy additions to the diet caused a definite increase in oxalic acid excretion.

3. No increase of the oxalic acid excretion could be demonstrated in cases of acute feeding disturbances.

#### METHODS

One reason that this subject has been so long neglected is that the methods of determination of oxalic acid in urine are so tedious and unsatisfactory.

This work was begun in 1905 at the suggestion of Professor Leo Langstein. The Autenrieth and Barth<sup>4</sup> method was used for the work done then. In this method the oxalic acid is thrown down as calcium oxalate; the oxalic acid is then isolated by heating with hydrochloric acid and dissolving in ether. An aqueous solution of the oxalic acid is finally obtained and reprecipitated with calcium chlorid. The precipitate is ignited and weighed as calcium oxid. The results were not published, as I found that the final precipitates contained phosphates.

The first part of the work presented here was done by the Salkowski method. In this method the urine is concentrated on the water-bath to one-third of its original volume, treated with concentrated hydrochloric acid, and the oxalic acid then dissolved in ether by shaking. As will be seen from the tables, this method gives lower results than the one devised by Albahary.<sup>5</sup> This is largely due to the difficulty of extracting all of the oxalic acid by shaking with ether. Although Salkowski advises shaking four times with ether, I found that the seventh wash ether still contained oxalic acid, and Albahary quotes Luzatto as saying that the eighteenth extraction still contained oxalic acid.

The Albahary method consists in adding sodium carbonate to the urine, and concentrating it to one-third of the original volume over the water-bath. This alkalization before heating has the advantage of preventing the volatilization as pointed out to us by Dr. Hall, or decomposition, of the oxalic acid which is so prone to occur when an acid solution of oxalic acid is heated. This concentrated solution is then treated with magnesium chlorid and ammonium chlorid and filtered to remove the phosphates. The filtrate is treated with calcium chlorid and acetic acid. The precipitate is removed and ignited. The amount of oxalic acid is then reckoned from the calcium oxid obtained. This method is much shorter and control experiments with definite amounts of oxalic acid show that more, though not all, is recovered by this procedure.

As there are no reported results of oxalic acid determinations in the urine of the new-born, they are shown in Table 1.

The results in Table 1 were obtained by the Salkowski method. The results shown in Table 2 were obtained by the Albahary method and are considerably higher.

If the results by the Salkowski method are averaged, we find a daily excretion of 2.75 mg., and by the Albahary method, 4.78 mg.

These were all normal breast fed new-born infants. The oxalic acid must therefore be endogenous. The quantities are distinctly larger than those found for older infants by Aaron and Franz.

Baby Ols. when 4 months' old showed by the Salkowski method 7.19 and 4.77 mg. per day oxalic acid excretion.

4. Autenrieth and Barth: *Ztschr. f. physiol. Chem.*, 1902, xxxv, 327.

5. Albahary, M.: *Compt. rend. Acad. d. sc.*, 1903, cxxxvi, 1681.

Harold R., 4 years old, with spasmophilia, gave a daily average by the Salkowski method from seventeen specimens, covering a period from October 31 to January 31, of 9.3 mg. Clifford Knick, 6 years old, with acute enteritis, enlarged tonsils, and adenoids, averaged 11.42 mg. for a period of eight days, also by Salkowski's method.

Violet Wall, aged 7 years, averaged by Salkowski's method, 10.53 for seven days during January. On January 10, she excreted 20.44 mg. On January 20 she was etherized for a tonsillectomy and the next day she excreted 0.45 mg. only, coming back to 13.25 on the following day.

TABLE 1.—OXALIC ACID DETERMINATIONS IN THE URINE OF THE NEW-BORN

Infant	Time Collected	Quantity c.c.	Oxalic Acid mg.
Sim. ....	First four days after birth...	146.5	3.59
Ols. ....	Second to fifth day after birth	248.5	4.94
Byr. ....	First four days after birth...	140.0	17.30
Hor. ....	Seventh day after birth.....	205.0	9.43
Hor. ....	Eighth day after birth.....	265.0	3.18

TABLE 2.—OXALIC ACID DETERMINATIONS BY ALBAHARY METHOD

Infant	Time Collected or Age	Quantity c.c.	Oxalic Acid mg.
Byr. ....	Fifth, sixth, seventh days after birth .....	307.0	15.50
Byr. ....	Eighth and ninth days.....	239.0	11.23
Shaw .....	Three days .....	168.0	13.47
Loog. ....	First seven days after birth..	334.0	12.35
Hay .....	Two days .....	89.0	18.01
Hay .....	Two days .....	39.0	12.35
Hay .....	Four days .....	34.0	23.81
Gusta .....	Four days .....	76.0	24.48
Reine .....	Five days .....	123.0	22.01

Dorothy Rub., aged 6 years, with bronchitis and adenoids, showed an average of 9.9 mg. for six days by the Salkowski method. Hilding Berg., 11 years old, with chronic cardiac valvular disease and rheumatic fever, gave the low average of 3.04 mg. for four days by the Salkowski method, and on one of these days no oxalic acid could be demonstrated in the urine. In the older children, also, the results by the Albahary method were definitely higher. Doris Russel, 6 years old, showed an average daily excretion of 21.6 mg. for six days. D. Sten., 2 years old, with a healed pleurisy, by the Albahary method, for a preliminary period of fourteen days, on a general diet, gave a daily oxalic excretion of 21.77 mg. For the next four days on an oxalic acid free diet the daily excretion averaged 16.42 mg. The last day of this period she excreted 5.62 mg. only. During the following four days she was given 50 c.c. of rhubarb sauce daily and her oxalic acid excretion increased to an average of 32.85 mg. per day. The amount of oxalic acid in rhubarb is given by Neuberg<sup>6</sup> as 2.4 gm. per kilogram of substance.

6. Neuberg, Carl: Von Noorden's Handbuch der Pathologie des Stoffwechsels, 1907, ii, 490.

## SUMMARY

The older methods of determination of oxalic acid are tedious and imperfect. The Albahary method gives better results and is much more rapid.

New-born infants excrete oxalic acid in the urine in varying amounts up to 9 mg. per day.

Older children excrete oxalic acid in considerable quantity, and one child, fed on rhubarb, showed a definite increase in oxalic acid excretion during the period of rhubarb feeding.

If we accept the usual figures which are given for the oxalic acid excretion in adults, given by Neuberg as from 15 to 20 mg., the excretion in children is relatively and at times absolutely higher.

## THE PHTHALEIN TEST IN ORTHOSTATIC ALBUMINURIA \*

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Orthostatic albuminuria is a comparatively common condition, especially in children, and has been the subject of frequent investigation, yet the pathology of the condition is far from being clearly understood. Although it is not commonly classified among the nephritides, actual opportunities for histologic examination of kidneys from individuals with orthostatic albuminuria, have been very infrequent, chiefly because of the benign character of the affection. Such opportunities for necropsy examination as have occurred have failed to reveal any of the usual pathologic findings of a nephritis. Until the accumulation of necropsy findings or physiologic experimentation shall have cleared up the pathogenesis of the condition, we must rely chiefly on clinical observation and renal tests for our knowledge of the factors involved in its production.

In a clinical investigation, the question of the integrity of the kidney function is naturally one of the first to suggest itself. A few earlier studies of kidney function in orthostatic albuminuria, using salt, potassium iodid, or indigo-carmin excretion, etc., as tests, have been made, but the results were indefinite and inconclusive. So far as I know, no tests of renal function have been made with the more delicate methods introduced in recent years, and hence this study was undertaken. In a preliminary note<sup>1</sup> I reported briefly the results of the phenolsulphonephthalein test in four cases, which are included in this paper.

Only marked cases of the so-called lordotic type were used in these studies—cases in which large amounts of albumin appeared in the urine after such a simple procedure as having the child stand against the wall for ten minutes with the heels and back of the head touching the wall, thus throwing the shoulders well back, and bringing the lumbar spine forward. In all these cases the urine was free from albumin after a night's rest in bed. Children with slight or moderate degrees of orthostatic albuminuria were not used for tests. In all

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\* From the Department of Pediatrics, Washington University, and the St. Louis Children's Hospital.

1. Read before the Washington University Medical Society, May 11, 1914; reported in the *Journal of the Missouri Med. Soc.*, June, 1914, and the *Bulletin of the Washington University Med. School*, June, 1915.

cases the albumin precipitated on the addition of acetic acid, although this precipitate was usually increased by heating. No casts were found in the urine.

The manner of making the tests was as follows: The cases were referred from among the children coming to the out-patient dispensary and admitted to the hospital for the carrying out of the tests. On admission, the children were kept in bed over night and the morning urine examined for albumin. If free, the child was placed in the position described above for ten or fifteen minutes, and the urine examined again. Cases then showing large amounts of albumin (enough to give a curdy precipitate with the acetic acid test), were utilized. The patient was again put to bed and the following day—the child meanwhile not being allowed up—a phenolsulphonephthalein test was made with the child in the position of accentuated lordosis throughout the whole time of the test. In the test 0.6 gm. of phenolsulphonephthalein contained in 1 c.c. of solution, was injected into the muscles of the back, as advised by Rowntree and Geraghty. The urine excreted in the first and second hour after injection was collected separately and the amount of phenolsulphonephthalein present in each estimated by means of a Du Boscq colorimeter. The children were then allowed to play about the ward for two or three days, an interval of time sufficient to get rid of the phthalein used in the first injection. On the third or fourth day, after the child had been in bed over night, the test was repeated with the child in the normal position, that is, lying flat in bed, not accentuating the lumbar curve. In some of the cases, the time of first appearance of the drug in the urine was noted, but not in all. The position of accentuated lordosis was maintained during the two hours required for the test by having the child lie on its back with several hard pillows under the lumbar spine, or by sitting in a chair, with a stick across the back, held in the crooks of the elbows. In three instances the order of the tests was reversed, the test in the normal position being made first, and in one case a longer interval elapsed between tests. The protocols are as follows:

#### PROTOCOLS

CASE 1.—Richard P. (No. 3828), aged 12 years, came to the dispensary in January, 1913, because of enuresis. He presented the typical findings of an orthostatic albuminuria, all other physical examination being negative except for an accidental heart murmur, which disappeared during the period of observation. The first phthalein test was made Feb. 19, 1913, with the patient in bed.<sup>2</sup> The first appearance of the drug was in five minutes, 62.8 per cent. being excreted in the first hour, and 5 per cent. in the second, or 67.8 per cent.

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2. It will be remembered that the drug normally appears in the urine in from five to eleven minutes after intramuscular injection, 40 to 65 per cent. being excreted in the first hour after the initial appearance, and 65 to 80 per cent. in two hours.

in two hours. The test Feb. 22, 1913, with the patient in the position of accentuated lordosis gave the first appearance in eight minutes, with 42.8 per cent. excreted in the first hour and 10 per cent. in the second, or 52.8 per cent. in the two hours; that is, 20 per cent. less in the first hour and 15 per cent. less in the two hours, than when he was in the normal position. April 11, 1914, the test was repeated, with the patient in the normal position, when 59 per cent. was excreted in the first hour and 5 per cent. in the second, or 64 per cent. in the two hours—a normal output, and no evidences of nephritis a year after the first tests.

CASE 2.—Blanche C. (No. 3302), 11 years old, came to the dispensary because of enuresis. Typical orthostatic albuminuria with no other abnormality. First phthalein test on May 4, 1914, with the patient in the position of accentuated lordosis. Time of appearance not noted. First hour, 39 per cent. excreted, second hour, 20 per cent., or 59 per cent. in two hours. Second test on May 5, 1914, with patient in the normal position. First hour, 48.8 per cent. excreted; second hour 10 per cent., or 58.8 per cent. in the two hours; that is, in the lordotic position 10.8 per cent. less in the first hour, but an equivalent amount in the two hours.

CASE 3.—Robert M. (No. 5027), 9 years old, came to the dispensary Feb. 18, 1914, because of enuresis and trachoma. Physical examination reveals no other abnormalities except an orthostatic albuminuria. Phthalein test March 11, 1914, in position of accentuated lordosis, showed first appearance in eight minutes, with 35 per cent. excreted in the first hour and 5 per cent. in the second, or 40 per cent. in the two hours. Phthalein test May 6, 1914, normal position, showed 66% per cent. excreted in the first hour, 20 per cent. in the second, or 86% per cent. in the two hours; that is, in the lordotic position, over 30 per cent. less for the first hour and 46 per cent. less for the two hours.

CASE 4.—Theodore K. (No. 3216), 10 years, came to the dispensary in May, 1910, because of hypertrophied tonsils and adenoids, with enuresis. He had, and still has, a typical orthostatic albuminuria, which has been observed now for over five years, with no further evidences of a nephritis. Subjected to the phthalein test May 2, 1914, in the position of accentuated lordosis. First hour, 41.2 per cent. excreted and in the second hour 10 per cent., or 51.2 per cent. for the two hours. Test repeated May 6, 1914, with boy in normal position, when 48.3 per cent. was excreted in the first hour, and 15 per cent. in the second, or 63.3 per cent. in the two hours. This case, therefore, shows approximately 12 per cent. less excreted for the two hours, and 7 per cent. less the first hour while in the lordotic position.

CASE 5.—John M. (No. 8192), aged 10 years, came to the dispensary because of urticaria and adenoids. No other abnormality except an orthostatic albuminuria. First phthalein test March 26, 1915, with boy in normal position. Time of appearance eight minutes. First hour, 55 per cent. excreted; second hour, 15 per cent. excreted, or 70 per cent. in two hours. Second phthalein test March 31, 1915, lordotic position. Time of appearance, eleven minutes. First hour, 30 per cent. excreted; second hour 40 per cent. excreted, or 70 per cent. in the two hours. In the lordotic position, 25 per cent. less was excreted during the first hour, but an equal amount for the two hours.

CASE 6.—Francis M. (No. 8317), aged 8 years, came to the dispensary because of an aphthous stomatitis. Typical orthostatic albuminuria in addition. First phthalein test April 16, 1915, in the lordotic position. Time of appearance, eight minutes. First hour 45 per cent. excreted, and second hour 15 per cent. excreted, or 60 per cent. in the two hours. Second phthalein test April 19, 1915, with boy in the normal position. First appearance, six minutes. First hour 60 per cent. excreted, second hour 10 per cent., or 70 per cent. excreted in the two hours. There was, therefore, 15 per cent. less excreted in the first hour and 10 per cent. less in two hours while in the lordotic position.



CASE 7.—Rosie T. (No. 8406), aged 11 years, came to the dispensary for bronchitis and orthostatic albuminuria. First phthalein test May 1, 1915, in normal position, showed 55 per cent. of the drug excreted in the first hour, and 12 per cent. in the second, or 67 per cent. in two hours. Second test on May 3, 1915, in the lordotic position, with 40 per cent. of the drug excreted in the first hour and 20 per cent. in the second, or 60 per cent. in the two hours. There was, therefore, 15 per cent. less excreted during the first hour in the lordotic position, and 7 per cent. less in the two hours.

CONTROL 1.—Frank R. (No. 3910), normal, well boy, subjected to the phthalein test Feb. 19, 1913, in position of accentuated lordosis and showed 56.5 per cent. excreted in the first hour and 15 per cent. in the second, or 71.5 per cent. in the two hours. Test repeated Feb. 22, 1913, with patient in the normal position, when 55 per cent. was excreted in the first hour and 15 per cent. in the second, or 70 per cent. in the two hours—approximately the same result in both positions.

CONTROL 2.—Alvin J. (No. 5572), aged 7 years, up and about the wards, with no urinary abnormality whatever. Subjected to the phthalein test in the position of accentuated lordosis May 6, 1914, and showed 76.8 per cent. of the drug excreted in the first seventy minutes (was unable to void at sixty minutes) and 5 per cent. in the next fifty minutes, or 81.8 per cent. in two hours. Test repeated with the boy in the normal position May 8, 1914, when 71.3 per cent. was excreted in the first hour and 12.5 per cent. in the second, or 83.8 per cent. in the two hours; that is, approximately the same for the two-hour intervals, but 5.5 per cent. more in seventy minutes, lordotic position than in one hour, normal position.

The accompanying table summarizes the results of the seven cases and controls.

It will first be noticed that all of the cases except Case 2, came within the limits of the normal as regards phthalein output when in the normal position. Case 2 is slightly under the average, but hardly enough to call the phthalein output abnormal. The seven cases averaged 69 per cent. output in two hours and 56.6 per cent. in the first hour. It was found, however, that when the child with orthostatic albuminuria maintained the lordotic position during the test, there was apparently a slowing up of the excretion of phthalein. This was most marked in the first hour, when the average for the seven cases was 39 per cent., in contrast to 56.6 per cent. in the normal position—a decrease averaging 17.6 per cent. The total difference for the two hours is less, averaging but 12.9 per cent. Moreover, it will be noted that in every instance this retardation occurs in the first hour, the extremes being 7.1 per cent. and 31.6 per cent., but that when the total for the two hours is contrasted, the retardation is less, and in two cases practically the same amount was excreted. It will be noted that in Case 3, the figures for the retardation are extreme, and much higher than the average. If this case is eliminated, the slowing taking place in the first hour and the increased excretion in the second hour, which brings the totals nearer for the two positions, is more

TABLE SHOWING PHTHALEIN EXCRETION IN LORDOTIC ALBUMINURIA CASES AND CONTROLS\*

Case	Position				Difference While in Lordotic Position		Remarks
	Normal		Lordotic				
	First Hour	Second Hour	First Hour	Second Hour	First Hour	Second Hour	
1	62.8	67.8	42.8	52.8	- 20.0	- 15.0	Appeared three minutes earlier in normal position.
2	48.8	58.8	39.0	59.0	- 9.8	+ 0.2	
3	66.6	86.6	35.0	40.0	- 31.6	- 46.6	Appeared three minutes earlier in normal position. Appeared two minutes earlier in normal position.
4	48.3	63.3	41.2	51.2	- 7.1	- 12.1	
5	55.0	70.0	30.0	70.0	- 25.0	0.0	
6	60.0	70.0	45.0	60.0	- 15.0	- 10.0	First hour, lordotic represents seventy minutes, instead of one hour.
7	55.0	67.0	40.0	60.0	- 15.0	- 7.0	
Average ....	56.6	69.0	39.0	56.1	- 17.6	- 12.9	
Control 1...	55.0	70.0	56.5	71.5	+ 1.5	+ 1.5	
Control 2...	71.3	83.8	76.8	81.8	+ 5.5	- 2.0	

\* Figures are in percentages.

striking. Thus, eliminating this case, an average of 15.6 per cent. less excretion takes place in the first hour, and a total decrease of 7.3 per cent. in two hours. A simple way of stating the finding is that cases of orthostatic albuminuria in bed excreted 56.6 per cent. of phthalein in the first hour and 12.4 per cent. in the second. In accentuated lordosis, a 39 per cent. output took place in the first hour and 17.1 per cent. in the second.

The normal control cases showed no change in elimination between the normal and lordotic positions.

If the above findings may be regarded as lending support to any of the various theories of pathogenesis, it would probably be that one which assumes a mechanical interference with renal circulation as the chief causative factor in the production of an orthostatic albuminuria. Jehle, who has been the most ardent advocate of this theory, believes that the accentuation of the normal forward curve of the lumbar spine so commonly seen in individuals with orthostatic albuminuria, produces an interference with the renal circulation either by compressing or stretching the renal vessels, or otherwise causing a congestion of the kidneys. He does not deny that vasomotor influences may affect the degree of albuminuria, but believes the mechanical factor to be the main feature, without which there is no orthostatic albuminuria. In support of his contention, he submits evidence to show that effacing the lordosis by postural methods causes a disappearance of the albuminuria, and that, furthermore, it is possible to produce an albuminuria in normal individuals by pressure directed through the abdominal walls against the great vessels, or, in animals, by directly constricting or compressing the renal vessels for a short time. Such methods would produce a retardation of the renal circulation, and would probably delay the excretion of a drug such as phenolsulphonephthalein.

#### SUMMARY

Renal function, as measured by the phenolsulphonephthalein test, in children with marked degrees of orthostatic albuminuria, is normal when the patients are at rest in bed. When these patients are placed in a position of accentuated lordosis, producing a marked albuminuria, the total output of phthalein in two hours is reduced—in the above seven cases, on an average 12.9 per cent. The most marked feature, however, is the retardation which takes place in the output during the first hour—the average of our cases being 17.6 per cent. less in the lordotic position. Normal children do not show this retardation and decreased elimination with the change of posture. If this retardation may be brought into relation with any of the theoretical ideas of the

pathogenesis of orthostatic albuminuria, it would probably be that which associates the condition with a decreased vascular supply to the kidney as the result of posture.

Metropolitan Building.

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# THE INFLUENCE OF CLOTHING ON THE SURFACE TEMPERATURE OF INFANTS \*

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## INTRODUCTION

The problem of high infant mortality in summer has received much attention, but of the various factors bearing on this problem, such as high outside- and room-temperature, humidity, etc., the factor of clothing has received relatively little attention. As a result of studies on puppies, we pointed out in a previous communication,<sup>1</sup> that the clothing may so seriously interfere with the loss of body heat at moderately high temperatures as to cause the death of the animal. Not that the necessity of scanty clothing for the infant at high temperatures has not been recognized, but it has never been the object of scientific inquiry. For the adult Rubner<sup>2</sup> has furnished very valuable data with regard to the prevention of heat loss by clothing, while for the infant no such data are available.

We therefore set out to furnish some more accurate data showing the influence of clothing on the heat regulatory power of the infant, particularly at high temperatures. For this purpose we determined the surface temperature of various parts of the infant, clothed and unclothed, at moderate and at high room temperatures. When clothed, the readings were taken on the surface of the clothing as well as on the corresponding skin area beneath the clothes. The rectal temperature of the infant and the temperature and humidity of the room were also recorded. With regard to the rate of heat loss by conduction and radiation, the determining factor in the clothed infant is the difference between the surface temperature of the clothes and the temperature of the surrounding air. In the case of the unclothed infant, the difference between the surface temperature of the skin and the temperature of the surrounding air is the determining factor.

## METHOD

The rectal temperature and room temperature were determined by means of mercury thermometers, the relative humidity by means of

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\* From the Otho S. A. Sprague Memorial Institute Laboratory of The Children's Memorial Hospital.

1. McClure and Sauer: Clothing as a Factor in the Production of Heat Stasis, *AM. JOUR. DIS. CHILD.*, 1915, ix, 490.

2. Rubner: *Lehrbuch der Hygiene*, 1907, Ed. 8.

wet and dry bulb thermometers. Because of its greater accuracy and adaptability we used the thermo-electric method<sup>3</sup> for the determination of surface temperatures. The apparatus consisted of a 300 ohm D'Arsonval ballistic galvanometer of the type built by Wm. Gaertner & Co. Copper wires connect the posts with the thermo-elements. These thermo-elements, two in number, were made by twisting together fine copper and constantan wires. With both of the thermo-elements at the same temperature there is no swing of the galvanometer. When one is kept at a constant temperature and the other exposed to a different temperature, an electric current is generated which causes a deflection of the mirror of the galvanometer. In our

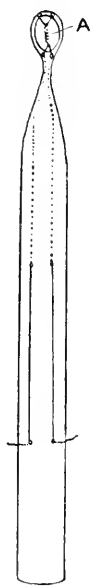


Fig. 1.—Applicator supporting thermo-element A.

work one of the thermo-elements was kept at a constant temperature in an ice bath, the other was supported in a suitable applicator by means of which it could be brought into contact with the surface the temperature of which was to be determined. The deflection of the mirror of the galvanometer was measured on a scale graduated in degrees centigrade. By means of a resistance box it was possible to obtain a constant deflection of the mirror from day to day under different room conditions. (Differences in room temperatures introduce

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3. We wish to express our thanks to Prof. Millikan of the Department of Physics of the University of Chicago for his suggestions and for the use of the apparatus.

slight changes in the thermo-electromotive forces at the binding posts, etc.) The applicator, as seen in Figure 1, was made of celluloid ( $20 \times 1.2 \times 0.2$  cm.) with an oval window at one end (1 cm. in its greatest diameter). The thermo-element used on the skin was suspended in the window, the celluloid forming the frame of the window was made as delicate as practicable in order to eliminate, as far as possible, heat loss from the surface of the skin by conduction through this material. This applicator was found to be especially convenient for taking skin temperature readings beneath the clothes. With the apparatus used it was possible to make readings showing a difference of 0.1 C.

#### THE EFFECT OF CLOTHING ON THE HEAT LOSS BY CONDUCTION AND RADIATION

First we studied the effect of the ordinary clothing on the heat loss of the infant by conduction and radiation. Three infants were studied: One normal breast-fed infant (wet nurse's baby), and two artificially fed infants which had recovered from minor ailments (Table 1). These infants wore the ordinary hospital clothing consisting usually of a thin cotton gown, double breasted cotton undershirt, cotton hose and diaper (cf. tables). Five minutes after bringing them into the examining room, temperature readings were made on the following parts: middle of forehead, right and left cheeks, the surface of the clothing over the sternum and abdomen, the skin surface of the sternum and abdomen beneath the clothing and the dorsum of each hand. Readings on the abdomen were made in the midline half way between xyphoid and umbilicus. The clothing was then removed and five minutes later readings were made over the skin of the same areas, and in addition on the dorsum of each foot. These readings were made at moderate (about 24.4 C.) and at high room temperatures (about 30.9 C.).

The loss of heat by conduction and radiation is proportional to the difference between the surface temperature of the body and the temperature of the surrounding air. In a clothed individual the temperature of the surface of the clothing must be taken as representing the surface temperature of that particular portion of the body in estimating the heat loss by conduction and radiation. Since the surface temperature of the clothing is lower than that of the bare skin of the same area of the child when unclothed (Tables 1 and 2), it approaches more nearly the temperature of the surrounding air, and the heat loss depending on conduction and radiation is less, therefore, in the clothed than in the unclothed infant. That clothing inhibits heat loss, as is well known, is further emphasized by the fact that the temperature of

TABLE 1.—SURFACE TEMPERATURES OF NORMAL—

No.	Name	Age in Mos.	Weight (Lbs.)	Diagnosis	Room		Rect. Temp.	Foreh.	Cheek	
					Temp.	Humid.			R	L
					C	%	C	C	C	C
1	Harriet C. ...	6	15¼	Breast fed.....	24.4	30	37.7	33.2	30.5	29.8
					25.	..	....	32.9	31.8	30.7
2	Harriet C. ...	6	15¼	Breast fed.....	24.4	26	37.7	32.5	30.7	30.5
					24.4	..	....	33.3	32.	31.6
3	Harriet C. ...	6	15¼	Breast fed.....	24.4	27	37.7	31.3	29.3	29.6
					25.	..	....	31.9	31.3	29.6
4	Albert D. ....	10	16	Recovered from mild diarrhea	23.3	28	37.	32.8	31.1	29.9
					23.3	..	....	32.1	30.6	30.7
5	Albert D. ....	10	16	Recovered from mild diarrhea	25.5	26	37.1	31.8	30.8	30.
					25.5	..	....	32.	30.7	30.1
6	Albert D. ....	10	16	Recovered from mild diarrhea	24.4	27	37.2	31.7	29.7	29.7
					24.4	..	....	32.	30.4	30.3
7	Leonard W.	7	15¾	Colored; convalescent tetany.	23.8	26	36.8	30.8	28.8	29.4
					23.5	..	....	31.4	29.4	29.4

TABLE 2.—SURFACE TEMPERATURES OF NORMAL—

No.	Name	Age in Mos.	Weight (Lbs.)	Diagnosis	Room		Rect. Temp.	Foreh.	Cheek	
					Temp.	Humid.			R	L
					C	%	C	C	C	C
1	Harriet C. ...	6	15¼	Breast fed.....	31.	32	37.5	33.7	31.6	31.6
					31.	..	....	33.3	32.9	32.7
2	Harriet C. ...	6	15¼	Breast fed.....	31.	21	37.4	33.	30.4	30.6
					31.	..	....	33.	32.4	32.4
3	Albert D. ....	10	16	Recovered from mild diarrhea	29.7	21	37.2	32.2	32.	30.6
					31.6	..	....	32.4	32.8	32.6
4	Albert D. ....	10	16	Recovered from mild diarrhea	30.5	35	37.1	34.3	33.5	33.5
					31.	..	....	34.3	33.9	34.3
5	Albert D. ....	10	16	Recovered from mild diarrhea	31.6	32	37.2	32.5	33.1	33.7
					31.	..	....	34.4	34.2	34.8



## —INFANTS AT MODERATE ROOM TEMPERATURES

Chest			Abdomen			Hand		Foot		Remarks
Over Clothes C	Under C	Bare C	Over Clothes C	Under C	Bare C	R C	L C	R C	L C	
29.5	35.5	....	30.7	35.2	....	32.9	33.3	....	....	Cotton undershirt (double breast). Cotton gown, hose, diaper.
....	....	33.4	....	....	33.6	32.5	30.9	30.7	30.7	Bare.
31.6	35.3	....	30.7	35.	....	32.	32.2	....	....	As in No. 1, but hose $\frac{1}{2}$ wool.
....	....	34.	....	....	33.8	32.7	31.8	29.5	29.8	Bare.
30.	34.2	....	30.1	35.1	....	31.6	32.2	....	....	As 2.
....	....	32.6	....	....	33.3	32.	29.6	28.5	29.5	Bare.
31.9	34.8	....	31.5	35.2	....	32.	31.8	....	....	Cotton undershirt (single breast). Cotton gown, diaper, $\frac{1}{2}$ wool hose.
....	...	33.	....	....	33.1	30.6	30.7	31.5	30.2	Bare.
31.	34.6	....	31.4	35.5	....	32.3	32.3	....	....	Cotton undershirt (double breast). Cotton gown, diaper, hose.
....	...	33.6	....	....	33.7	31.7	31.7	31.7	31.3	Bare.
31.3	34.6	....	31.5	35.7	....	32.6	32.3	....	....	As 1.
....	....	33.6	....	....	34.4	32.3	32.3	32.9	32.8	Bare.
27.6	33.1	....	28.4	34.1	...	31.8	31.6	....	....	$\frac{1}{2}$ wool double breast undershirt. Cotton gown, hose, diaper.
....	....	32.5	....	....	33.1	30.	30.	28.2	27.6	

## —INFANTS AT HIGH ROOM TEMPERATURES

Chest			Abdomen			Hand		Foot		Remarks
Over Clothes C	Under C	Bare C	Over Clothes C	Under C	Bare C	R C	L C	R C	L C	
31.8	35.	....	32.7	36.1	....	32.9	32.7	....	....	Cotton undershirt (double breast). Cotton gown, hose, diaper.
....	....	33.3	....	....	33.7	32.5	32.1	31.	31.	Bare.
30.8	35.4	....	30.4	35.8	....	33.8	32.	....	....	$\frac{1}{2}$ wool undershirt, hose. Cotton gown, diaper.
....	....	33.6	....	....	34.	33.	32.2	32.2	32.4	Bare.
30.	34.	....	32.	35.4	....	32.4	32.6	....	....	As No. 1.
....	....	34.	....	....	34.6	32.6	31.8	32.6	32.4	Bare.
32.7	35.3	....	32.9	36.8	....	33.3	32.7	....	....	$\frac{1}{2}$ wool undershirt, cotton gown, hose, diaper.
....	....	33.3	....	....	35.7	34.5	33.9	34.3	33.3	Bare.
33.3	36.1	....	34.4	36.7	....	34.2	33.5	....	....	Cotton gown, diaper, $\frac{1}{2}$ wool undershirt, hose.
...	....	35.4	....	....	35.8	34.2	34.2	33.3	33.5	Bare.

the skin beneath the clothing is higher than that of the same area when unclothed (see Tables 1, 2, 8).

The accompanying diagram (Fig. 2) has been constructed from Tables 1 and 2. It shows the difference in temperatures between the air and the bare skin of the chest, in the first place, and the air and surface of the clothing over the chest, in the second place. Bars I and II show the average differences in temperature of the chest of the unclothed child and the air, and of the clothing over the chest of the clothed child and the air, respectively. Bars I and II represent these differences at moderate room temperature (24.4 C.); bars III and IV represent similar differences for the observations made at the high room temperature (30.9 C.). To be more explicit, for Bar I the average surface temperature over the bare chest was 33.2 C., the average room temperature 24.4 C., a difference of 8.8 C. For Bar II the aver-

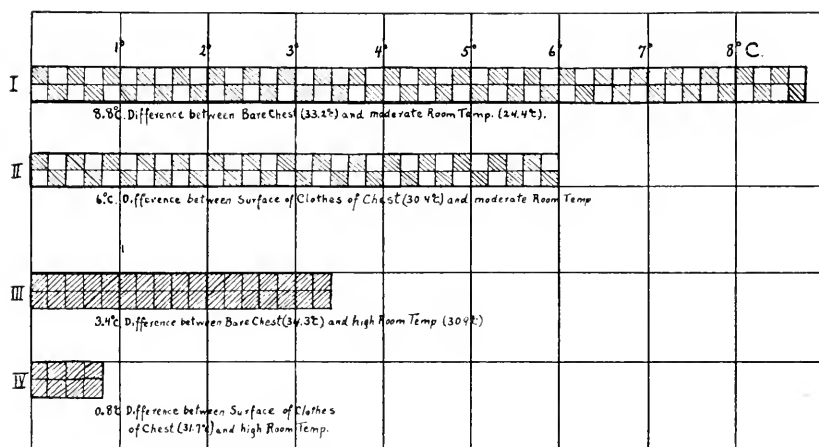


Fig. 2.—Diagram of temperature differences.

age temperature over the clothing on the chest of the clothed infant was 30.4 C., the average room temperature 24.4 C., a difference of 6 C. For bar III the average surface temperature of the bare chest of the bare infant was 34.3 C., the temperature of the room 30 C., a difference of 3.4 C. For bar IV the average surface temperature over the clothes on the chest was 31.7 C., the average room temperature 30.9 C., a difference of 0.8 C.

It is evident that the difference in temperatures of the surface of the body and the room alone does not permit an exact determination of the amount of heat loss by conduction and radiation. At the same time it must be admitted that the heat loss is proportional to this difference. A comparison, therefore, of the differences represented by Bar I and II, and III and IV gives us an indication as to what extent

TABLE 3.—SURFACE TEMPERATURES OF NORMAL, UNCLOTHED INFANTS AT MODERATE ROOM TEMPERATURE  
(From Table No. 1, except Cases 8, 9)

No.	Name	Age in Mos.	Weight (Lbs.)	Room T.		Humid.		Rect. T.		Foreh.		Cheek		Chest		Abdom.		Hand		Foot		Remarks
				°C	°F	%	°C	°C	°F	°C	°F	R	L	C	C	R	C	R	L	R	L	
1	Harriet C. ....	6	15¼	25.		30	37.7	32.9		31.8	30.7	31.8	30.7	33.4	33.6	32.5	30.9	30.7	30.7	30.7	30.7	Normal, breast fed, awake but quiet.
2	Harriet C. ....	6	15¼	24.4		26	37.7	33.3		32.	31.6	32.	31.6	34.	33.8	32.7	31.8	29.5	29.5	29.8	29.8	Normal, breast fed, awake but quiet.
3	Harriet C. ....	6	15¼	25.		27	37.7	31.9		31.3	29.6	31.3	29.6	32.6	33.3	32.	29.6	28.5	29.5	29.5	29.5	Normal, breast fed, awake but quiet.
4	Albert D. ....	10	16	23.3		28	37.	32.1		30.6	30.7	30.6	30.7	33.	33.1	30.6	30.7	31.5	30.2	30.2	30.2	Recovered from mild diarrhea.
5	Albert D. ....	10	16	25.5		26	37.1	32.		30.7	33.	30.7	33.	33.6	33.7	31.7	31.7	31.7	31.7	31.3	31.3	Recovered from mild diarrhea.
6	Albert D. ....	10	16	24.4		27	37.2	32.		30.4	30.3	30.4	30.3	33.6	34.4	32.3	32.3	32.9	32.8	32.8	32.8	Recovered from mild diarrhea.
7	Leonard W. ...	7	15¼	23.5		26	36.8	31.4		29.4	29.4	29.4	29.4	32.5	33.1	30.	30.	28.2	27.6	27.6	27.6	Colored, convalescent tetany, moderate rickets.
8	Richard M. ...	..	..	22.		33	37.1	31.2		29.2	29.2	29.2	29.2	33.	33.2	27.6	27.5	28.	28.4	28.4	28.4	Slight discharge from right ear.
9	Fay M. ....	11	14	25.5		24	37.4	32.7		31.1	31.1	31.1	31.1	34.6	34.5	30.9	30.1	31.9	31.1	31.1	31.1	Convalescent tetany.
Average.....				24.3		27.4	37.3	32.2		30.7	30.3	30.7	30.3	33.3	33.6	31.1	30.5	30.3	30.2	30.2	30.2	

TABLE 4.—SURFACE TEMPERATURE OF ATROPHIC, UNCLOTHED INFANTS AT MODERATE ROOM TEMPERATURE

No.	Name	Age in Mos.	Weight (Lbs.)	Room T. C	Humid. %	Rect. T. C	Foreh. C	Cheek		Chest C	Abdom. C	Hand		Foot		Remarks
								R C	L C			R C	L C	R C	L C	
1	Harriet J. ....	6	7½	23.8	28	36.7	34.	32.4	32.9	34.6	33.5	32.6	31.3	31.1	30.2	Atrophic; awake, but quiet.
2	Evelyn G. ....	2½	4	23.8	25	36.7	34.2	32.4	32.9	35.4	35.8	31.9	31.3	27.1	26.9	Atrophic; awake, but quiet.
3	Vern B. ....	4	4½	25.	24	37.3	34.1	33.3	33.9	35.1	34.5	32.7	31.3	32.3	32.1	Atrophic; pyelocystitis (only occasional flareups of temp.); awake, but quiet.
4	Vern B. ....	4	4½	25.5	..	35.4	33.6	33.3	33.9	34.9	34.6	32.9	32.1	32.7	32.4	Atrophic; pyelocystitis (only occasional flareups of temp.); awake, but quiet.
5	Vernet G. ....	3½	4¾	25.	28	37.2	33.5	32.3	33.1	34.4	35.	30.3	29.9	30.1	29.7	Atrophic; awake, but quiet.
6	Helen P. ....	4	6¾	23.8	26	36.6	33.6	32.2	32.8	34.	34.4	32.1	31.2	32.4	32.4	Atrophic; awake, but quiet.
7	Marie A. ....	3	5¾	23.8	26	35.4	34.	32.8	33.4	34.2	34.	31.5	32.1	32.5	32.8	Atrophic; awake, but quiet.
Average.....				24.4	26.1	36.5	33.9	32.9	33.3	34.7	34.6	32.	31.3	31.2	30.9	

TABLE 5.—SURFACE TEMPERATURE OF OTHER INFANTS WITH INANITION. BARE AT MODERATE ROOM TEMPERATURE

No.	Name	Age in Mos.	Weight (Lbs.)	Room T. C	Humid. %	Rect. T. C	Foreh. C	Cheek		Chest C	Abdom. C	Hand		Foot		Remarks
								R C	L C			R C	L C	R C	L C	
1	Evelyn E. ....	2½	6¾	23.8	24	36.8	32.4	32.	32.6	33.4	33.8	32.	31.8	32.4	32.4	Pyloric stenosis.
2	Robt. H. ....	3	6¾	23.3	..	35.4	33.4	32.1	31.7	32.6	33.2	29.1	28.8	28.5	29.5	Pyloric stenosis.
Average.....				23.6	24	36.1	32.9	32.1	32.2	33.	33.5	30.6	29.9	30.5	31.	

the heat loss by conduction and radiation is influenced by clothing at the respective room temperatures. If we let Bar I equal 100 then Bar II would equal 68.2; likewise, if we let Bar III equal 100, then Bar IV would be equal to only 23.8.

If we accept these figures, with all due reservation, as the basis of calculation for the heat loss by conduction and radiation, it would then become evident that the clothed infant at a moderate room temperature is capable of availing itself of about 68 per cent. of the possible heat loss due to these factors. At the high room temperature it can only avail itself of about 24 per cent. of this possible heat loss, and this in spite of the fact that the surface temperature of the bare chest at the

TABLE 6.—AVERAGES  
Bare at Moderate Temperatures

	Normal	Atrophy	Pyloric Stenosis
Room temperature.....	24.3 C	24.4 C	23.6 C
Room humidity.....	27.4%	26.1%	24 %
Rectal temperature.....	37.3	36.5	36.1
Forehead.....	32.2	23.9	32.9
Right cheek.....	30.7	32.9	32.1
Left cheek.....	30.3	33.3	32.2
Chest.....	33.3	34.7	33
Abdomen.....	33.6	34.6	33.5
Right hand.....	31.1	32	30.6
Left hand.....	30.5	31.3	29.9
Right foot.....	30.3	31.2	30.5
Left foot.....	30.2	30.9	31

high room temperature is 1.1 C. higher than at the moderate room temperature. The rectal temperature is about the same at both moderate and high room temperatures. The rise of the skin temperature favors heat loss by conduction and radiation, but this is more than counteracted by the clothing.

The surface temperature of the clothing over the chest averaged about 2.7 C. lower than the surface temperature of the chest of the unclothed infant. This difference was about the same at moderate and at high room temperatures. Judging from these data we would expect the clothed child to cease losing heat from this area by conduction and radiation in a surrounding temperature of about 2.7 C. lower than would the unclothed infant. With the high room temperature the

clothed child approaches rapidly the point where heat loss by conduction and radiation is no longer possible.

Heat loss, due to evaporation from the body surface, has not received attention in this study; and the question might be raised, therefore, whether the inhibition of heat loss by conduction and radiation due to clothing, might not be compensated for by an increase of evaporation. Against this supposition we find that the surface temperature of the skin beneath the clothing is higher than that of the skin of the same area unclothed, the difference averaging over the chest 0.9 C. for the moderate room temperatures and 1.4 C. for the high room temperature. If evaporation was sufficiently increased to compensate for the decreased heat loss due to inhibition of conduction and radiation, we would expect no such increase of surface temperature under the clothing.

TABLE 7.—TEMPERATURE OF CHESTS OF NORMAL INFANTS  
(From Tables 1, 2)

No.	A. Moderate Room Temperature				B. High Room Temperature			
	Room Temp. C.	Bare C.	Over Clothes C.	Under Clothes C.	Room Temp. C.	Bare C.	Over Clothes C.	Under Clothes C.
1	25	33.4	29.5	35.5	31	33.3	31.8	35
2	24.4	34	31.6	35.3	31	33.6	30.8	35.4
3	25	32.6	30	34.2	30.5	34	30	34
4	23.3	33	31.9	34.8	31	35.3	32.7	35.3
5	25.5	33.6	31	34.6	31	35.4	33.3	36.1
6	24.4	33.6	31.3	34.6	....	....	....	....
7	23.5	32.5	27.6	33.1	....	....	....	....
Aver.	24.4	33.2	30.4	34.6	30.9	34.3	31.7	35.2

#### SURFACE TEMPERATURE IN DISEASE

In the course of our work we made surface temperature readings on infants with various types of inanition (atrophy and pyloric stenosis). The children were brought into the examining room, all of the clothing was removed, and after five minutes the surface temperatures were read. We give below the data obtained from the two groups of these cases (Tables 4 and 5). In order to compare these with the findings in the normal infant, we have constructed Table 7. The findings in the cases of atrophy, in which the rectal temperatures were considerably lower than in the normal infants, were rather surprising in that all the surface temperature readings showed a higher

average than those for the corresponding surfaces of the normal infants. This higher surface temperature, causing greater heat loss, would lend support to the findings of Schlossmann,<sup>4</sup> Bahrdt and Edelstein,<sup>5</sup> and Murlin and Hoobler,<sup>6</sup> who have shown by calorimetric methods that the metabolism of the atrophic infant proceeds at a higher level than that of the normal infant. In seeking an explanation for the cause of this high surface temperature, the thinness of the subcutaneous tissue seemed to offer a ready explanation. That this is not the entire explanation, however, is indicated by the surface temperature readings of the pyloric stenosis cases (Table 5), in which emaciation was also very marked. The surface temperature readings approximated very closely those of the normal infant.

We also made temperature readings in a variety of diseases including infections such as pneumonia, cystitis, otitis media, etc., but from the small number of such cases, no conclusions can be drawn at this time.

#### CONCLUSION

At a room temperature of about 31 C. an infant, clothed in the manner above described and under the conditions of our observations, approaches very closely the point where a heat loss by conduction and radiation is no longer possible. Our experiments with puppies indicate that such a state of affairs may be fraught with danger to the organism.

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4. Schlossmann: *Ztschr. f. Kinderh.*, 1912-13, v, 227.

5. Bahrdt and Edelstein: *Festschrift, Dr. Otto Heubner*, Berlin, 1913.

6. Murlin and Hoobler: *The Energy Metabolism of Ten Hospital Children Between the Ages of Two Months and One Year*, *AM. JOUR. DIS. CHILD.*, 1915, ix, 81.

# THE AMMONIACAL DIAPER IN INFANTS AND YOUNG CHILDREN \*

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ST. LOUIS

## I

Several years ago I was asked to see a little girl, 17 months old, suffering from a severe dermatitis of the diaper region. The skin of the buttocks, perineum, genitals, thighs, and lower abdomen was severely inflamed and numerous vesicles and blebs were scattered over this area. The infant appeared perfectly well otherwise. The mother stated that the diaper removed that morning had a very strong odor, "just like ammonia." She had saved the diaper in a closed receptacle. On unfolding the wet diaper, a very strong penetrating odor of ammonia was noticed. So strong was this gas that it irritated my eyes very disagreeably during the examination. It seemed clear to me that the skin lesions were induced by the ammonia in the urine, since ammonia is a powerful rubifacient and vesicant.

This case served to interest me in the study of ammonia in the urine and the resulting lesions, and for many years facts in regard to this condition were collected and form the basis for this study. The term *ammoniuria* was used to designate the presence of free ammonia in the urine, as well as the skin lesions produced by this irritant.

## CLINICAL PHENOMENA

The ammoniacal diaper is frequently encountered by the practitioner. Usually, the odor of ammonia is faint, especially in young infants. Only occasionally does the concentration become sufficiently intense to produce the characteristic irritation of the skin. The severest grade occurs in infants between 1 and 2 years of age.

The lesions consist of inflamed areas on the inner side of the thighs, the genitals, the buttocks and lower abdomen. Sometimes the whole diaper region shows a diffuse redness.

More characteristic is the appearance of vesicles and blebs. There may be only one at the end of the prepuce; often this is associated with others on the prominent parts of the genital region. It is the parts which come in direct contact with the diaper which show the blisters. Rarely the whole diaper region may show numerous confluent blisters. No vesication may be observed, but after the intense

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congestion, sometimes the whole epidermis becomes hard, cracked, and the skin seems covered with thin parchment. The dead skin separates in a flaky desquamation.

A very important lesion to which no attention has been given by pediatricists, is the formation of a blister at the meatus. This occurs only in boys who have been circumcised. The prepuce protects the meatus in the uncircumcised. The blister ruptures and a superficial ulceration remains. This causes distress in urinating and may be the source of hemorrhage. The ulcer is exceedingly troublesome at times. It becomes covered by a thin crust, which may partially or entirely occlude the orifice of the urethra, so that urination is painful and difficult. The passage of the urine removes the crust and the ulcer is irritated again by the urine. Healing, therefore, may take several weeks.

The skin lesions nearly always appear in the morning when the infant has lain for a long period during the night. Infants who do not wet the diaper are not subject to this trouble. In fact, enuresis and ammoniuria go together. The assumption that the enuresis depended on the ammonia in the urine was entertained for awhile; the reverse is probably true.

The ammoniacal diaper is a frequent precursor of pyelocystitis in female infants. The irritated genital region becomes more susceptible to infections. On account of the protection afforded by the labia, the urethral orifice in the female is not subject to the blistering.

The association of the ammoniacal diaper and the exudative diathesis is frequent. The irritating urine initiates patches of eczema in the diaper region, which are exceedingly intractable unless the urinary condition is relieved.

The onset is usually abrupt and the course is very irregular and indefinite. The irritating urine may be present for one day only; then, it may last for weeks.

#### ILLUSTRATIVE CASES

CASE 1.—C. C., girl, aged 8 months; fed on dextrinized flour and milk; has had a tendency to eczema on the face. Lately she has been very irritable and urinates frequently. She is rather constipated, but the nutrition is very good. The mother noticed that the diaper every morning had a strong odor like ammonia. There is considerable irritation of the buttocks, but no blistering.

CASE 2.—B. C., boy, aged 4 years, has nocturnal enuresis. The mother has observed a very strong odor of ammonia. This morning she detected blood stains on the sheets, which alarmed her. Examination revealed the glans penis congested, and an ulcer covered by a crust at the meatus.

CASE 3.—R. D., boy, 1 year old, has been artificially fed since birth. His nutrition is very good at present. His diet consists of whole cows' milk, cereals, bread, custard, orange juice, apple sauce and prune juice. He is usually constipated. He passes much urine through the night; the bedding is soaked in the

morning. Considerable irritation of the genital region has been present for the last two days. This morning the whole prepuce was swollen and edematous, and a large blister is present on the dorsum. Another vesicle is found on the inner side of the thigh. The bedding has a very strong odor of ammonia.

As the ulcer would not heal, after ten days the family had the boy circumcised. After the operation the ammoniuria continued. The head of the penis and wound edges became irritated, swollen and a large blister formed on the glans penis. He had difficulty in urinating and a crust formed at the meatus. The urine continued to give this strong ammoniacal odor for several weeks longer, so that the little boy became known as the "ammonia factory." Treatment had no effect.

CASE 4.—C. A., boy aged 23 months; on a general diet; passed about half a teaspoonful of blood after urinating. The glans penis showed ulceration and a crust covered the meatus, occluding the opening. The mother said the urine was very strong.

CASE 5.—J. P., 2 years old, boy, has always been well. Was breast fed to 11 months. Was seen first in February, 1915. Because he has been housed too much, he looked pale and appetite was poor. He was on a general diet. Was suffering from incontinence of the urine. Clothes wet all the time. He was restless at night. During the last week mother noticed severe irritation of the genital region. One blister was found on the scrotum and the urinary meatus showed an ulceration. The mother observed an ammoniacal odor of the bed clothes. Bowels rather constipated.

CASE 6.—S. L., boy, aged 2 years. Was operated on for adenoid vegetations one week ago. The mother noticed a remarkable penetrating odor of ammonia in the diaper, which alarmed her very much. Very slight genital irritation.

The boy was on mixed diet. Has had recurrent attacks of intestinal indigestion. The mother noticed a similar odor one year before when she changed her washwoman. She was directed to supervise the rinsing of the diapers and the odor from the diapers disappeared.

#### ETIOLOGY

Ammonia in the urine of infants and young children has been observed by pediatricists. The ammoniacal diaper has become a well-known term, following the suggestion of Southworth. In St. Louis this condition is very frequent. While we pass over the cases in which a slight ammoniacal odor of the bedding is noticed, in the last five years, I have collected brief notes of seventy-eight cases, in all of which the patients showed some skin lesions, and the ammonia was sufficiently intense to warrant more than a passing notice.

Of these seventy-eight cases, fifty-four, or about three-fourths, occurred in children over 10 months of age. The worst cases are observed, not in infants, but in young children, from 1 to 4 years of age. By far the greater number of cases occur in the winter months.

The severest lesions in my series have occurred in boys. As already mentioned, pyelocystitis, not infrequently, follows the occurrence of severe ammoniacal condition in girls. It seems to me this predisposing cause to pyuria should be given more attention.

While several infants were fed partially on the breast, the disorder seems to be almost limited to artificially-fed infants. The severest

grades arise at the time when the infant is beginning to take solid food. Mixtures containing cow's milk and cereal decoctions are especially prone to result in the ammoniacal diaper. Taking large quantities of bread was etiologically related in a few cases. Egg also seemed to be a disturbing factor.

Several careful tests were made to determine the effect of orange juice. In three infants the mothers insisted that the ammoniacal odor was stronger when orange juice was given. Repeated tests in one little girl showed that the diaper was ammoniacal when orange juice was given, and had little odor when the juice was omitted.

High percentages of fat in the milk seemed provocative of this disorder in young infants. The removal of the fat from the food had very little effect on the ammonia in older infants.

Buttermilk, casein-buttermilk, whole milk, and condensed milk stood etiologically related in some cases.

The majority of the infants were constipated; often the stools were reported normal.

The administration of alkalies often aggravated the condition; no relief was observed from their use.

The disorder usually came on suddenly and disappeared as mysteriously. Sometimes it lasted one or two days; at other times, several weeks. Recurrent attacks were frequently observed.

The only disorder apparently connected with this phenomenon was the exudative diathesis, eczema, asthma, etc.

## II

For several years I have been trying to ascertain the cause of this trouble. After satisfying myself that this emanation from the bedding was really ammonia (by holding a splinter dipped in hydrochloric acid over the diapers), the further origin of this gas was pursued. That the ammonia was not due to bacterial activity was shown by the fact that the odor was perceptible in a very short time after the urine was passed. Then the odor was different, in that the offensive odor of decomposed urine was absent.

Since Keller discovered that infants with digestive disturbances have a great increase in the ammonia content of the urine, it was at first assumed that the ammoniuria really was a symptom of an acute indigestion, although the clinical symptoms by no means corroborated this view. At any rate, following out the theory of an enterogenic acidosis, the cases were treated by the restriction of fats and the administration of alkalies; but this therapy was so disappointing that it was evident that our theory was erroneous.

We (Dr. Coffin, Dr. Koessel and myself) made numerous tests to determine the concentration of the ammonia in the urine. We availed ourselves of the very simple method described by Rosenbloom<sup>1</sup> of determining the ammonia nitrogen in the urine. Dr. Koessel, at first, made a series of tests in the Bethesda Foundling Home. His results are given in Table 1. The figures give the cubic centimeters of decinormal sodium hydroxid used in titrating 10 c.c. of urine after the addition of neutral potassium oxalate (first column) and after the addition of formic aldehyd (second column). By multiplying the figures in the last column by 0.0014, the quantity of ammonia nitrogen in 10 c.c. of urine may be obtained.

TABLE 1.—ESTIMATE OF AMMONIA NITROGEN IN 10 C.C. URINE OF BETHESDA BABIES

Case	First Titration *	Second Titration	Remarks
1 .....	3.5	2.5	
2 .....	1.0	1.0	
3 .....	1.0	0.8	
4 .....	3.1	4.9	Intoxication
5 .....	1.3	1.3	
6 .....	1.6	1.2	
7 .....	1.5	2.6	Diarrhea
8 .....	2.0	1.1	
9 .....	2.4	1.6	
10 .....	3.8	3.1	Constipation
11 .....	1.3	0.6	
12 .....	0.8	0.3	
13 .....	1.7	1.2	
14 .....	2.2	0.9	
15 .....	3.4	1.6	
16 .....	2.4	8.4	Green Stools
17 .....	1.6	0.8	
18 .....	3.8	7.0	Intoxication
19 .....	3.5	2.1	
20 .....	3.7	3.8	Intoxication
21 .....	6.3	6.0	Diarrhea
22 .....	2.2	1.1	

\* The figures give cubic centimeters decinormal sodium hydroxid. Infants less than 1 year of age.

It will be seen that the concentration of ammonia nitrogen in infants is not high, as a rule, yet infants with digestive disturbances show a high percentage of ammonia nitrogen in the urine.

Then Dr. Coffin made a series of tests on older children who presented themselves at the clinic or office. The results are shown in Table 2.

1. Rosenbloom, J.: Clinical Methods for Estimation of Total Nitrogen and Ammonia Nitrogen in Urine, Jour. Am. Med. Assn., 1913, lxi, 87.

The ammonia nitrogen in children is relatively higher than in infants. Occasionally a surprisingly high figure may be obtained without apparent cause.

We have examined the urines of a few children who have shown symptoms of ammoniuria. Obviously, the urine which caused the irritation could not be examined. These figures are given in Table No. 3.

TABLE 2.—AMMONIA NITROGEN IN URINES OF OLDER CHILDREN

Initials	Age Years	First Titration	Second Titration	Diagnosis
F. S. ....	1	3.7	7.2	Marasmus
A. W. ....	3	2.3	3.9	Enuresis
W. W. ....	13	6.3	7.4	Bronchitis
F. P. ....	4	2.3	3.9	Vaginitis
R. S. ....	1	3.6	0.3	P a r t i a l starvation
F. N. ....	6	5.1	4.0	Neuritis
A. L. ....	10	11.5	9.5	Acute indiges- tion
M. E. ....	.....	5.3	4.3	
J. M. ....	$\frac{3}{4}$	3.1	1.9	Malnutrition
L. K. ....	11	4.5	6.9	Enuresis
M. B. ....	5	2.0	2.2	Hemorrhagic nephritis
E. G. ....	3	5.6	3.3	Pyelitis
V. W. ....	3	3.6	3.0	Acute nephri- tis
L. B. ....	2	3.5	2.6	Healthy
S. B. ....	6	4.1	4.2	Enuresis
S. S. ....	3	5.3	8.9	Asthma
H. F. ....	6	4.2	5.4	
M. S. ....	4	4.6	4.8	Enuresis
S. S. ....	6	6.1	4.6	Enuresis
S. H. ....	.....	1.5	1.2	
E. S. ....	.....	4.0	4.0	Enuresis
E. W. ....	4	3.9	3.7	Eczema
F. H. ....	1	4.0	4.2	Mucous colitis
R. S. ....	2	7.0	5.8	Indigestion
D. B. ....	5	4.6	2.7	
W. D. ....	3	5.4	6.9	Anorexia
B. M. ....	2	1.5	2.8	Cystitis
J. P. ....	2	4.5	3.1	
A. P. ....	2	8.0	3.6	

As will be seen, the ammonia content is rather high, but not higher than in some other children who did not present the symptoms.

As the concentration of the total solids might account for the variation in the figures, we compared the specific gravity with the ammonia content. Table No. 4. In general, a high ammonia content is found in the urine with high specific gravity.

We made a few tests to ascertain what effect rest and activity have in the ammonia content. Table No. 5.

TABLE 3.—SHOWING THE ACIDITY AND AMMONIA IN THE URINE OF CHILDREN WHO HAD THE SYMPTOMS OF AMMONIURIA

Initials	Age Years	First Titration	Second Titration
H. B. ....	2	6.9	5.8
E. G. ....	3	5.6	3.3
L. B. ....	2	3.5	2.6
E. D. ....	3	4.6	5.1
A. J. ....	2	5.4	4.8
R. S. ....	1	7.0	5.8
J. P. ....	2	4.5	3.1
S. L. ....	2	2.0	2.2
E. J. ....	2	3.3	6.0
S. L. ....	2	2.0	2.4

TABLE 4.—SHOWING QUANTITY OF AMMONIA IN THE URINE OF CHILDREN, AS COMPARED WITH THE SPECIFIC GRAVITY

Initials	Age Years	First Titration	Second Titration	Specific Gravity
A. L. ....	9	11.5	9.5	1.025
H. S. ....	8	2.2	2.4	1.010
P. A. ....	5	6.2	4.8	1.014
P. A. ....	5	1.7	2.4	1.022
S. H. ....	3	1.5	1.2	1.020
E. W. ....	4	4.6	3.9	1.020
R. S. ....	2	4.0	2.7	1.014
D. D. ....	6	4.4	4.0	1.015
P. G. ....	2	3.2	4.9	1.012
H. S. ....	8	1.4	1.7	1.008

TABLE 5.—SHOWING THE DIFFERENCE IN THE ACIDITY AND AMMONIA CONTENT IN THE URINE PASSED AFTER A NIGHT'S REST, AND LATER DURING THE DAY

Initials	Age Years	First Titration	Second Titration	Diagnosis
P. A. (rest)...	4	6.3	7.4	Nephritis
(active) .....		4.0	5.3	
A. S. (rest)...	9	2.8	3.0	Orthostatic albuminuria
(active) .....		3.5	2.8	
A. J. (rest)...	1	6.3	7.2	Ammoniuria
(active) .....		3.0	2.5	
A. R. (rest)...	9	4.0	4.5	Cystitis
(active) .....		3.1	4.7	

This was suggested by the fact that the morning diaper is the one usually showing the strongest odor of ammonia. It is curious that all but one of the patients so examined showed the ammonia nitrogen higher in the morning after the night's rest. As a rule children who have the symptoms of ammoniacal urine have a high content of ammonia nitrogen in the morning urine.

But this by no means solves the difficulty. This ammonia is combined with acids, but the clinical evidence proves that the ammonia, which causes mischief, is *free* ammonia. We thought at first that the young child, under certain conditions, passes free ammonia, and thus arose the term ammoniuria. While it is clear enough that free ammonia gas was arising from the diaper, we never could obtain a specimen of urine in a vessel or bottle which gave off free ammonia, except in traces. We could not prove, in a single instance, that a child ever passes ammonia in its free state.

It is only recently that I succeeded in demonstrating the origin of the free ammonia in two cases. It is not necessary to give the details. The immediate cause of the ammoniacal diaper is the presence of an alkali in the diaper or bedding.

This fact was tested at the bedside and at the laboratory. When the diaper, which has been washed in a strong alkaline soap, is not thoroughly rinsed in clear water, sufficient alkalinity remains in the cloth to decompose the ammonia in the urine. This is the origin of the "common" saying that strong soap or lye in the diaper blisters the baby. It is not the alkali or soap on the skin, but the ammonia produced, which causes the skin irritation. An alkaline stool mixed with urine acts the same way, and we have often attributed an intertrigo to irritating feces, when it was really caused by ammonia.

It is clear that the neutral or nearly neutral urine would be the most dangerous, since a highly acid urine would neutralize all the alkali before the ammonium salts would be decomposed.

This fact also explains the failure of dieting and the administration of alkalies. It would explain the action of orange juice, since this makes the urine less acid. Its more frequent occurrence in older children, its occurrence in the winter months, and the irregular course, are easily explained when we adopt this theory. One mother told me that her baby invariably passed ammonia after a certain woman washed the diapers. Another mother had no more trouble when she was told to oversee the washing of the nursery bedding.

In St. Louis, on account of the high content of lime in the water, it is possible that this alkaline earth may be a possible cause in certain babies, since in drying the bedding considerable lime would remain.

CONCLUSIONS

Free ammonia in the diapers of young children is a frequent condition.

If much ammonia is present, severe irritation and vesication of the diaper region may occur.

The ammonia is derived from the ammonium compounds in the urine, and is liberated by an alkali present in the diaper—soap, lye, lime, or stool.

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# CLINICAL DEPARTMENT

## ACUTE MYELITIS FOLLOWING VARICELLA

REPORT OF A CASE \*

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It is believed that almost any of the infectious diseases may attack the central nervous system to produce encephalitis or myelitis. The following is a list of those mentioned: Typhoid fever, typhus fever, erysipelas, malaria, variola, measles, acute rheumatism, severe puerperal infections, scarlatina, influenza, pneumonia, pertussis, dysentery, cholera, gonorrhea, streptococcus and staphylococcus infections. Only one author (Councilman) has in recent years mentioned varicella as a possible cause. The case that I am now reporting bears such a close relationship to an attack of varicella that I consider it of sufficient interest to record.

*History.*—The patient, R. T., a white boy, 7 years of age, applied for treatment at the dispensary of the Harriet Lane Home, Aug. 17, 1914, complaining of "stiff knees."

*Family History.*—Unimportant.

*Personal History.*—The patient was a full term child, following a normal delivery. He was breast fed for eighteen months, and cut his first tooth at seventh month. There was an abscess behind the left ear at the eighth month, which was not serious, and pertussis at 5 years. These were the only two illnesses that he had had, and with these two exceptions, the patient has always been a healthy child.

*Present Illness.*—Ten weeks before, June 1, 1915, the patient had an attack of varicella, just after his older brother had recovered from a similar one. He had the usual papulovesicular eruption which was very wide-spread.

Eight weeks before, June 14, 1915, or two weeks after the onset of varicella, the patient's temperature began to rise, and his mother noticed that his legs were drawn up. It was further discovered that he was unable to move either of his legs or his left arm. There was also loss of sensation over these parts, which was more marked over the left leg than over the right. This last condition persisted for two weeks, and sensation gradually returned again. His left arm was held over his head, and he would scream with pain if one attempted to pull it down or to straighten out either of the legs.

A few days after the onset of these symptoms, the child suffered with retention of urine and was catheterized twice. This was followed by incontinence of both urine and feces. This incontinence continued for six or seven weeks. On the first application, or eight weeks after the attack, it was found that under ordinary conditions the sphincter control was good; however, the urine could not be long retained.

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\* Submitted for publication Oct. 8, 1915.

The patient was admitted to the Harriet Lane Home, August 19, 1914.

*Physical Examination.*—The child was undernourished but did not look sick. His head, heart, lungs, abdomen and genitalia were apparently normal.

The knees were flexed and the legs could not be entirely straightened. The muscles were soft and perhaps slightly atrophied. Both knee-kicks were hyperactive, the right more so than the left. There was an ankle clonus on both sides, which was better sustained on the right. The muscular strength was good and equal in the arms. The legs were very weak, though they could be moved fairly well voluntarily. Sensations of touch, pain, and temperature were apparently normal. There was some hyperesthesia of both legs.

Of laboratory findings, the von Pirquet skin test was questionably positive, the spinal fluid normal, and the Wassermann negative in both spinal fluid and blood. The eyegrounds were found to be normal.

Sept. 4, 1914, the patient was discharged from the hospital, improved.

Oct. 2, 1914, he returned to the dispensary. He was able to walk slowly and with some difficulty, with both his knees somewhat flexed. The steps were short and the feet were dragged along the floor. He was still suffering with urinary incontinence if there was any delay in reaching the toilet. There was, however, no incontinence of feces.

On physical examination the legs looked thin, as though some atrophy had taken place. The tendon reflexes were still greatly increased. Babinski's test was positive on both sides. There was an ankle clonus present on the right.

Aug. 5, 1915, one year after the first admission, the patient appeared greatly improved and was able to play freely. There was still some definite spasticity noticeable in the lower extremities, best brought out after running or walking rapidly. He was able to extend his legs normally. The tendon reflexes were hyperactive as before, and the Babinski was positive on both sides. There was no ankle clonus, and no evidence of urinary incontinence except at night, a condition which had existed prior to his illness.

The occurrence of these symptoms indicated unmistakably a definite lesion in the cord. They followed so closely on an infection with varicella that it seems justifiable to consider these two conditions as having a definite relationship, especially as there was an absence of any external condition to which might be assigned an etiologic significance.

# PROGRESS IN PEDIATRICS

## RESUME OF THE RECENT LITERATURE ON RESPIRATORY DISEASES \*

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### EXAMINATION OF THE CHEST

Wood<sup>1</sup> believes that the present method of percussion is of little value, because there is no universal standard. He has found that percussion notes can be determined with fair accuracy on the basis of pitch alone. The difference in pitch between normal resonance and flatness is about two octaves. These notes are easily acquired by a little practice by whistling or humming the note percussed. He also believes that the lungs should be percussed from below upward as the normal lung is more apt to lie below, while disease is more common at the apex.

Bauer<sup>2</sup> has found that cases of typical acute food intoxication all showed hyperresonance and an increase of lung area which could be demonstrated, the anterior border reaching to the sixth or seventh rib, overlapping the heart, the posterior border reaching to the eleventh or twelfth dorsal vertebra. Patients who recovered showed a diminution of the size of the lungs.

Mielke<sup>3</sup> has noted a dulness at the apex of the lungs which is due to the weakness of the muscles and faulty posture, and which disappears on making the patient stand erect.

### BACTERIOLOGY

Tunncliff<sup>4</sup> has found an organism which is apparently the cause of acute rhinitis. It is a delicate, curved, gram-negative, anaerobic bacillus which is found in the early stages of acute rhinitis before it becomes purulent. It somewhat resembles a spirochete but is probably a bacillus. She found it in 79 cases of acute coryza, 8 times in pure culture, but in only 5 out of 63 smears from the normal nose. It produced rhinitis in man and in dog. It was not found in purulent

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\* Submitted for publication Nov. 6, 1915.

1. Wood, N. K.: Jour. Am. Med. Assn., 1914, lxiii, 1378.

2. Bauer, F.: Monatschr. f. Kinderh., 1914, xii, 510.

3. Mielke: Berl. klin. Wchnschr., 1914, p. 1218.

4. Tunncliff, Ruth: Jour. Infect. Dis., 1915, xvi, 493.

secretions, nor in scarlet and diphtheria. In chronic nonpurulent rhinitis it was found in 17 of 18 cases. It was twice obtained from the sputum in bronchitis.

In an effort to find the cause of coryza, Kruse<sup>5</sup> made a Berkefeld filtrate of the dilated nasal secretions of persons suffering with coryza. The filtrate was bacteria-free. When this filtrate was applied to the nasal mucosa of healthy persons it caused an acute coryza in seventeen out of fifty-four cases. The incubation was one to four days, usually two or three days. In some cases there was also bronchitis. He concludes that the cause of at least one form of coryza and coughs belongs to the ultramicroscopic group of organisms.

Cecil<sup>6</sup> has found that the *Streptococcus viridans* can be isolated from practically all mouths and throats. It is the most common organism found in the infected tonsil. It was also found in all cases of pyorrhea studied, in five out of twelve cases of coryza, and in three cases of sinus disease. In bronchitis eight out of fourteen cases showed a predominance of this organism. All of the viridans infections are mild, but tend to become chronic, are followed by little or no immunity, and hence tend to recur. Vaccine therapy is valuable to prevent recurrence.

Brückner, Gaetgens and Vogt<sup>7</sup> believe that the influenza bacillus is not a harmless saprophyte, but that it is very frequently the cause of respiratory infections in children. The influenza infections tend to relapse, and often become chronic.

Holt<sup>8</sup> believes that the influenza bacillus is definitely pathogenic in many respiratory infections. As a rule it has not a high degree of virulence, but in exceptional instances this may be the case, and it may cause a general infection. In the Babies' Hospital, the *Bacillus influenzae* was found in 30 to 40 per cent. of the sputum cultures made in the last five years. Pneumococcus was found in 62 to 87 per cent., streptococcus, 29 to 46 per cent., and staphylococcus, 76 to 90 per cent. The belief of many pathologists that the influenza bacillus is not pathogenic is refuted by finding it in pure cultures in meningitis. In influenza infections the wide fluctuation of temperature is the most characteristic feature. This is seen in pneumonia, otitis, cases with few catarrhal symptoms, as a complication of tuberculosis, and in cases resembling whooping-cough. Diagnosis between spasmodic cough in influenza and whooping cough can at times be made only with great difficulty. The blood count differs in the two

5. Kruse, W.: München. med. Wchnschr., 1914, lxi, 1547.

6. Cecil, R.: Laryngoscope, 1915, xxv, 97.

7. Brückner, Gaetgens and Vogt: Jahrb. f. Kinderh., 1912, lxxvi, 417.

8. Holt, L. E.: Arch. Pediat., 1914, xxi, 724.

conditions, influenza giving a polymorphonuclear percentage of 60 to 70. Prognosis in uncomplicated influenza is good. When it complicates pneumonia, the course is likely to be greatly protracted. Relapses are common in all influenza infections. These cases should be carefully isolated as they are very contagious. They improve rapidly if they can be moved to a warm climate or with the advent of warm weather.

Chappell and Brown<sup>9</sup> call attention to the great frequency and extreme seriousness of respiratory infections in infants' wards. These infections are more serious than common contagious diseases and more difficult to control. The pneumococcus and streptococcus infections cause most of the trouble. Staphylococcus and influenza are also frequently found. They attempt to prevent respiratory infections by increasing the child's resistance by attention to its nutrition, by careful nursing and by postnasal douching. A special syringe was used which throws the stream forward through the nasal cavity. Argyrol, boric acid and peroxid solutions were used. The ward in which this douching was carried out twice a week for each patient, showed a distinctly smaller number of infections than the control ward in which there was the same class of cases. [Further experience with this method at the Babies Hospital has not seemed to bear out the earlier results.]

#### STRIDOR

Rach<sup>10</sup> enumerates as the varieties of stridor:

1. Nasal stridor, which is snuffling, seen in coryza and adenoids, and which disappears when the nostrils are occluded.
2. Pharyngeal stridor, which is snoring, as seen in greatly enlarged tonsils, and scarlet fever, diphtheria, tonsillar or retropharyngeal abscess.
3. Laryngeal stridor, which is crowing, and is seen in pertussis, laryngospasm in tetany, diphtheria of the larynx, pseudocroup, measles, and local laryngeal conditions, i. e., tuberculosis, tumors, edema, or stenosis after intubation.
4. Endothoracic stridor with Roentgen-ray findings:
  - a. Thymic stridor, which is congenital or begins in the first month, is inspiratory, constant, and rattling, bleating or clucking. There is dulness over or alongside the sternum. The Roentgen ray shows asymmetrical widening of the middle shadow, usually to the right, but occasionally to the left. The lateral view shows the shadow in the usual clear retrosternal space. Thymic hypertrophy may exist without stridor, but when it co-exists it seems to have a causal relation.

9. Chappell, W. F., and Brown, A.: *AM. JOUR. DIS. CHILD.*, 1914, vii, 380.

10. Rach, E.: *Ztschr. f. Kinderh.*, 1914, xi, 1.

Congenital stridor, due to abnormal softening of the laryngeal cartilages, gives the same type as the thymic stridor. [This type (Thomson's) might better be classified under laryngeal stridor.]

b. Stridor from enlarged bronchial lymph nodes. This is expiratory, regular, loud, and moist, the inspiration being almost noiseless. There is cough, which is shrill, with overtones, and there are apt to be attacks of suffocative dyspnea. V. Pirquet test is positive. There is occasional edema of the face, exophthalmus and dilated veins of the face and chest. A dullness over the sternum or between the scapula and bronchi, bronchophony from the first to fourth dorsal vertebrae. (In this respect see the view of Stoll (*AM. JOUR. DIS. CHILD.*, December, 1912) who believes that whispered bronchophony is not significant unless heard below the fourth dorsal vertebra.) The Roentgen-ray shadows are discrete, rounded, sharply outlined beside the tracheal bifurcation.

c. Stridor from an abscess from carious vertebrae. This may be inspiratory or expiratory; cough and cry are dull and weak. V. Pirquet is positive; the Roentgen ray shows diseased vertebra and there are other symptoms of spondylitis.

d. Asthmatic stridor, in which there is prolonged expiration with piping or rattling sounds, the thorax becoming fixed in the inspiratory condition. There is fever and apathy and great dyspnea. V. Pirquet is negative (v.i. Rongel), the Roentgen ray shows the diaphragm to be low and almost immobile. The hilus shadows may be thickened.

e. Stridor from tracheal displacement, due to fibrosis, fluid, tumors, etc. This gives no characteristic symptom, but can be recognized with the Roentgen ray.

#### BRONCHITIS AND ASTHMA

Kerley<sup>11</sup> believes that recurrent bronchitis in children is due to faulty metabolism. It occurs in children who have a history of difficult feeding, many of whom are subject to eczema, recurrent vomiting, migraine, etc. His experience leads him to believe that fat and cane sugar are badly borne by all these children, and he thinks it is the inability of the child to oxidize these high energy foods which gives the predisposition to this group of conditions. His treatment is the complete withdrawal of cane sugar. The child is allowed no cow's milk or only small amounts of skimmed milk. Clothing must be of medium weight; warm baths at bed time followed by vigorous rubbing are useful. The bowels must be carefully regulated. Bicarbonate of soda and salicylates and occasionally arsenic are administered. In

11. Kerley, C. G.: *Arch. Pediat.*, 1914, xxxi, 741.

his hands this treatment gives a very good result in 95 per cent. of the cases.

Rachford<sup>12</sup> believes that migraine, recurrent vomiting, recurrent sibilant bronchitis, coryza, asthma and urticaria are all closely related to food intoxications and are curable by dietetic treatment. The foods allowed include beef, mutton, fowl and fish, cereals, bread, vegetables (except tomatoes), cooked fruits, skimmed milk and thick soups. The foods forbidden are sweets, butter fats, eggs, raw fruit, salads, shell fish, tea, coffee, pastry, gravies, cod liver oil and alcohol. After the child has been on the above diet for some time one egg a day is allowed. Gradually other forbidden articles are added and the child is watched to see if symptoms recur. The bowels are regulated by magnesium salts. A great deal of fresh air is insisted on, especially at night. Alkalies are given in the form of sodium bicarbonate, or potassium citrate, for a period of from six to eight weeks. During the attack the tincture of belladonna (2 to 4 minims) is given three times a day. This treatment will control the syndrome in almost every instance, and is also useful in preventing recurrent vomiting or migraine.

Florand, Francoise and Flurin<sup>13</sup> believe that the character of chronic bronchitis is not explicable by the kind of infection, nor by disturbances of circulation, but depends on a diminished resistance which amounts to a veritable weakness of the bronchi. They have found three symptoms in the interval between the recurrent attacks. There is hyperesthesia of the mucous membrane to differences of temperature. Cold air excites cough and slight dyspnea. There are variations in the circulation which give congestion and swelling in the mucous membrane. This results in functional disturbances of the nose, larynx or bronchi. There is also hypersusceptibility to the factors which tend to increase secretions.

Hutinel<sup>14</sup> believes that asthma in infants is not so often due to odors, powders, emotions, etc., but more often to catarrhal conditions following coryza, hypertrophied adenoids and tonsils, bronchitis, or bronchial adenopathy. Eighty per cent. of the cases give a family history of asthma, migraine, obesity, urinary or biliary lithiasis. Children subject to asthma often have migraine in later life. The asthma is the result of a nervous reaction due to a hypersensibility of the respiratory nerves, causing a spasm of the bronchial muscles. There is a predisposition in certain subjects which is either hereditary, or comes from a special temperament, in some cases lithemic, in some

12. Rachford, B. K.: *Arch. of Pediat.*, 1914, xxxi, 488.

13. Florand, Francoise and Flurin: *Ref. in Ztschr. f. Kinderh.*, 1914, viii, 476.

14. Hutinel: *Rev. gén. de clin. et de therap.*, 1914, xxviii, 23.

cases anaphylactic. Tuberculosis may coexist with asthma, in spite of the general belief that this does not occur. He recommends hygienic treatment, cold baths and the administration of iodids.

Rongel<sup>15</sup> quotes the conclusions of Soca after the examination of 700 asthmatics, that asthma is a bulbar neurosis, the result of an hereditary predisposition depending on varying influences. It is often secondary to infectious disease and also to chronic diseases (cardiopathy, anemia, etc.). Even when secondary it needs treatment as an independent condition, as treatment of the primary disease often accomplishes nothing. Asthma is often a symptom of tuberculosis. Soca found that two-thirds of his cases of asthma had tuberculosis; the frequent coexistence of the two conditions makes it seem possible that asthma is the reaction to tuberculosis in some persons. To try out this theory Rongel tested 100 asthmatics under 16 years of age. Fifty per cent. gave positive V. Pirquet reactions. In the remaining 50 per cent. it was not possible to prove any tuberculosis by V. Pirquet or by examination. These figures go far to disprove the old theory that asthma and tuberculosis rarely exist in the same person. The importance of exposure is shown by the following:

Cases with	V. Pirquet
Tuberculous antecedents .....	32 + 16—
Asthmatic antecedents .....	11 + 29—
Neither tuberculous nor asthmatic antecedents .....	7 + 16—

[These observations of Rongel and Soca make it evident that the asthmatic is at least as susceptible to tuberculosis as other children. It seems as if the existence of a chronic bronchitis would offer a fertile soil for the implantation of the tubercle bacillus.]

Manirloff<sup>16</sup> sensitized animals with serum of an asthmatic patient, and later injected a solution of Charcot-Leyden crystals, producing death with symptoms of anaphylaxis. The controls, sensitized with normal serum, show no symptoms after injection of the solution of Charcot-Leyden crystals or of normal sputum solution. He believes that the Charcot-Leyden crystals are derived from proteins and that asthma is a pure manifestation of anaphylaxis.

Talbot<sup>17</sup> reports six cases of asthma, traceable directly to eggs, all of which gave urticarial reaction to egg albumin rubbed on the unbroken skin or on a V. Pirquet scarification. The wheal appeared in a few minutes and lasted half an hour. If the reaction is repeated too often, asthmatic attacks may be precipitated. He found that some of his cases were sensitized to other proteins, as horse serum, pollen,

15. Rongel, A.: *Arch. de méd. des enf.*, 1913, xvi, 95.

16. Manirloff: *Centralbl. f. Bakteriöl.*, 1912, lxiii, 564.

17. Talbot, F.: *Boston Med. and Surg. Jour.*, clxxi, 708.



etc. He believes that either the sensitization or a tendency to it may be transmitted from mother to child, and this has been proved to be possible in animals. Many, if not all, cases may be immunized to egg by giving small amounts of egg albumin in capsules and gradually increasing the dose. It must be started far below the patient's limit of tolerance and gradually increased, about a milligram a day or less. When the egg idiosyncrasy is cured the asthma stops. It is better to immunize such a patient against egg albumin than to allow him to run the risk of accidentally getting egg in some cooked food, and in that way become acutely ill.

Schloss<sup>18</sup> studied with great care a child who was sensitized to several different proteins—egg albumin, oatmeal, almonds, and other like foods. A great many others were tested but the child reacted only to those distinct groups. He was cured by giving ovomucoid in 2 milligram doses in capsules, gradually increased.

Mathews<sup>19</sup> has found that 90 per cent. of 300 cases of asthma were relieved by removing the cause of chronic suppuration in the nose and retention of nasal secretions. Drainage gave relief in proportion as it was possible to make it complete and free. The pus and mucus, whether sterile or infected from the antra of asthmatic patients, injected into guinea-pigs, sensitized them, and a second dose caused anaphylactic shock. Asthma with hay fever comes on first only on exposure to an irritant; later without this contact. Some other substances must have developed the possibility of acting as an antigen. On account of the relief obtained from drainage of diseased nasal conditions, he believes that the sensitizing agent may be the retained and autolyzed secretions of the nose or nasal sinuses.

Ephraim<sup>20</sup> discusses very thoroughly the theories of asthma. It has been the generally accepted view that asthma is a neurosis, but it is dangerous to state positively that any condition is a pure neurosis, for so many diseases formerly so classified have been proved by newer methods of investigation to have a genuine organic basis. The following reasons have been advanced for classifying asthma as a neurosis:

1. Its appearance in attacks; but this is also true of many organic conditions of long standing, which give symptoms only in acute attacks.
2. The sudden onset of attacks; but really the attacks do not come on suddenly as do convulsions, paralysis, and other nervous phenomena. Actually, asthma comes and goes more gradually. Even granting

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18. Schloss, O. M.: *AM. JOUR. DIS. CHILD.*, 1912, iv, 341.

19. Mathews, J.: *Trans. Assn. Laryngol., Rhinol. and Otol.*, 1913, xix, 62.

20. Ephraim, A.: *Verhandl. d. Verein Deutsch. Laryngol.*, 1913-14, p. 79.

the sudden onset, it signifies no more than a secondary excitation of the nervous system starting from a diseased organ.

3. The relatively healthy aspect of the asthmatic is supposed to indicate its functional nature. This is not always true, but even if true, it merely indicates that no destructive organic illness exists, and does not exclude an organic condition.

4. The asthmatic shows signs of other nervous conditions. This is not the observation of most clinicians, but when other neuroses exist they are probably the result of the wearing illness.

5. It has been regarded as a diseased condition of the respiratory center itself. Results of all recent research, however, have shown that there is no single respiratory center, but merely scattered muscle centers, not anatomically but only synergically united. The stimulation of no center or tract will produce asthma. A contraction of the bronchi can be caused by stimulation of the vagus or trigeminus but none of the characteristics of true asthma are produced, i. e., the rhonchi, the secretion, and the typical breathing. These do not appear in severe spasm of the bronchi, caused by anaphylactic poisoning, muscarin, etc. Strychnin poisoning, even when it causes death by suffocation, does not resemble asthma in the least. Stimulation of the nasal mucosa produces asthma, but only in asthmatics in whom there is already a predisposition to it. Stimulation of the nasal mucosa in normal persons merely produces sneezing, lacrymation or coughing, even when the stimulation is intense. It is therefore the asthmatic disposition which renders the attacks of asthma possible.

That there is a real organic basis for asthma is shown by the following:

1. Attacks come on in sleep when the nervous system is at rest.
2. Catarrhal processes precede and induce the attack.
3. The effects of nitrites and iodids, substances which have not the least effect on the nervous system.
4. The sputum, which is thick, tenacious and rich in cells.
5. Necropsy findings regularly show changes in the bronchi.
6. Fever occurs fairly often.
7. The occurrence of asthma in localized areas of the lung.

The one thing lacking to complete the picture of an organic disease in the bronchial mucosa is the continuity of the disease which we are accustomed to see in all organic conditions. Where there is a chronic bronchitis we have the tie which joins one attack to another, but where there are apparently healthy intervals it is more difficult to find this tie.

Ephraim has found that when an endobronchial application of epinephrin is made on an asthmatic in an absolutely free interval, the reaction is different from that in a healthy patient. In the asthmatic

there is an expectoration of a sticky, gray sputum, which was not present before, and which does not appear in a normal person. Microscopically this sputum shows small gray, thread-shaped plugs, suspended in a clear mucus, which resemble ciliated bronchial epithelium. These cells do not stain well, but appear necrotic, and show that there must be a chronic desquamative process present in the asthmatic, even when we can discover no symptoms, and this constitutes the asthmatic disposition. The causes which transform this symptomless chronic catarrh to an asthmatic attack are numerous. As internal causes, he recognizes anything which causes an increased congestion of the bronchi, i.e., horizontal position in sleep, overloading the stomach, abnormally deep breathing, as in coughing and laughing. As external causes, anaphylaxis, idiosyncrasy against spices, odors, etc., overloading the blood with carbon dioxide, reflex and psychic nervous factors. The nerve centers are in a state of increased irritability which is a secondary, definite irradiation to the segments corresponding to the bronchial nerves. The psychic element is merely accidental as in all other diseases of an organic nature, as cardiac disease, tuberculosis, etc. In nasal reflex asthma, the irritable membrane may be related to Head's zones of irritability on the skin in visceral diseases.

In discussing Ephraim's paper Killian believes that there is a form of asthma directly due to nasal hyperesthesia, a form which starts regularly from the bronchi, and a mixed form. Hyperesthesia alone is not enough to start the attacks, but there must be a predisposition, and an excitability of the nervous system. Patients can have hay fever from three to five years before asthmatic attacks begin. The hay fever gradually produces the nervous irritability which is necessary to cause asthma.

[It is evident that there are two distinct view points from which the nature of asthma is considered. Certain cases are definitely the result of anaphylaxis to eggs, serum, pollen or other foreign proteins. Other cases occur in patients who have chronic or recurrent bronchitis and there is no evident relation to anaphylaxis. It is possible that the sensitizing protein in the second group of cases is derived from the bacteria present in the air passages, or from changes in the proteins of the secretions in the air passages, which render the individual's own protein toxic. It may well be that the two types of asthma are quite distinct and that bronchial spasm is merely a condition which may be excited by various causes. For a discussion of the relation of asthma and anaphylaxis see Zinsser, H., *Infection and Resistance*, McMillan, New York, 1914, p. 434.]

Pirie<sup>21</sup> reported twenty-five cases of bronchitis and asthma, treated with autogenous vaccines. The bacteria used were pneumococci, streptococci, staphylococci, and Friedlander's bacilli. Nearly all were mixed

21. Pirie: *Brit. Med. Jour.*, 1913, 1268.

infections. The vaccines were given up to the point at which a mild reaction was produced. Of the chronic bronchitis cases seven were cured, four moderately improved, and four improved slightly. In nine cases of asthma two were cured and five considerably improved.

Borch<sup>22</sup> recommends a proprietary preparation of pituitary gland, which in most cases relieved the attacks and often prevented recurrences in his hands. He noted unpleasant effects in three children between 11 and 13 years, difficult breathing and collapse. Care should be taken in administration of this remedy in children.

#### BRONCHOTETANY

Lederer<sup>23</sup> describes a new syndrome which appears in the course of tetany. In spasmophilic children, sometimes as the only symptom, sometimes with other signs of this condition, the bronchial muscles become tonically contracted. The smallest branches of the bronchi are affected most and the alveoli supplied by them are shut off from the outside air. The air imprisoned thus is gradually absorbed so that the affected parts of the lung become atelectatic. A condition of edema supervenes (as in the extremities in carpopedal spasm), and the lumina of the alveoli and bronchi become filled with fluid. He observed this condition in 10 per cent. of his cases of tetany.

His clinical picture is as follows: In the course of a definite tetany, following other symptoms, or occasionally preceding them, increasing dyspnea calls attention to the lungs. There is dulness at the bases combined with tympany above, and over the dull areas is heard high-pitched bronchial breathing with râles. There is an irregular temperature. The dyspnea gradually increases, the patient becomes cyanosed and dies of suffocation. The course may be sudden and shortly fatal, or may come and go over a longer period, but all of his patients died. The diagnosis, if tetany is manifest, is not difficult, but when the bronchial spasm appears as the first symptom, it may be puzzling until other manifestations appear. The signs over any one area may come and go in the protracted cases. The Roentgen ray should differentiate this condition from pneumonia, showing scattered areas of atelectasis. [The reproduction of his roentgenograms are very poor and show very little. It is doubtful whether the differentiation can be easily made from bronchopneumonia by the Roentgen ray.]

At necropsy areas of atelectasis 0.5 to 2 centimeters in diameter are found, sometimes fusing to occupy an entire lobe; there is compensatory emphysema of the rest of the lung. Section shows empty collapsed alveoli, normal bronchi, full blood vessels and no sign of

22. Borch, I.: *Therap. d. Gegenw.*, 1913, liv, 536.

23. Lederer, R.: *Ztschr. f. Kinderh.*, 1913, vii, 1.

inflammatory reaction. The treatment in his hands was entirely unsatisfactory, as the cases were nearly all too rapid. He recommends human milk, phosphorus, cod liver oil, and carbohydrates. Lederer suggests for this condition the name of "*Bronchotetanie*."

Rietschl<sup>24</sup> reports a case of mild tetany with slightly increased electrical irritability and the peroneus phenomenon, which had recurrent attacks of severe dyspnea. Over the right upper lobe there was moderate dulness and prolonged expiration and rhonchi but no bronchial breathing. The case was thought to be bronchitis with a small patch of pneumonia. The attacks of dyspnea were considered to be asthmatic at first, but against this diagnosis were the signs of the right apex. There was no eosinophilia and epinephrin did not relieve the symptoms. Under treatment with calcium, phosphorus, cod liver oil, the patient gradually recovered. He considers this a case of mild bronchotetany on account of the electrical reactions, the local signs of the lungs and the spasmodic dyspnea. Although the differentiation from pneumonia and asthma is very difficult, he suggests that possibly many so-called asthmatic cases may be bronchotetany. He also divides the cases of asthma in infants into two distinct classes: true asthmatic attacks, which are rare, and cases of recurrent bronchitis with asthma. He has never seen asthmatic bronchitis change into true asthma in children.

Wieland<sup>25</sup> reports cases of bronchotetany and concludes that it is a definite clinical picture in certain severe cases of spasmophilia. It can be diagnosed only by the Roentgen ray shadow which causes a blurring of the lung structures resembling that seen in atelectasis. The prognosis is bad. A milder form, however, exists, which may recover.

Breuning<sup>26</sup> demonstrated a specimen from a case of bronchotetany. There had been a history of convulsion and mild catarrhal symptoms without fever. This was followed by sudden attacks of dyspnea in one of which the child died. At necropsy there was a small amount of pneumonia in the right lower lobe. The rest of the lung showed atelectatic areas with compensatory emphysema. Although this was not a clear case, on account of the presence of pneumonia, he considers it to have been a case of bronchotetany.

#### LOBAR PNEUMONIA

During the last three years the workers at the Rockefeller Institute have reported epoch-making researches on pneumonia (Cole and

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24. Rietschl, H.: *Monatschr. f. Kinderh.*, 1913, xii, 261.

25. Wieland, E.: *Monatschr. f. Kinderh.*, 1915, xiii, 205.

26. Breuning: *Ref. in Ztschr. f. Kinderh.*, 1914, viii, 253.

Dochez,<sup>27</sup> Dochez and Gillespie,<sup>28</sup> Cole,<sup>29</sup> Dochez and Avery<sup>30</sup>). They have found that pneumococci can be definitely divided into groups by their immunologic reactions and by their agglutination with immune serums. By these means they recognize four distinct types of organisms.

Type 1 is composed of pneumococci which are responsible for about 38 per cent. of all cases of acute pneumonia. They are moderately virulent, and develop an immune serum which protects mice against any one of the organisms belonging to the type. This serum also agglutinates all of the group.

Type 2 also produces a serum which gives a high grade of passive immunity, and which agglutinates all the pneumococci of the type. This type is more virulent than Type 1.

Type 3 consists of the *Pneumococcus mucosus* (*Streptococcus mucosus*). There are several closely related races of this type of organism which show cross agglutination, but which do not cause the development of an immune serum. This group is the most virulent of all. The organism is characterized by its thick capsule and by the very thick mucus produced in infections which it causes.

Type 4 is a heterogeneous number of organisms each of which apparently differs from every other. Each one develops a serum which protects against itself, but not against any other pneumococcus. There is no cross agglutination.

The occurrence of the different types in cases of pneumonia is as follows:

	Occurrence, Per Cent.	Mortality, Per Cent.
Type 1 .....	38	25
Type 2 .....	30	36
Type 3 .....	11	47
Type 4 .....	21	6

The incidence and mortality of the various types does not seem to vary greatly from year to year. The same types are found in Boston and Philadelphia, and with about the same relative frequency. There has been no evidence of the change of any organism from one group to another, no matter how long it has been cultivated on artificial mediums, nor after passage through many generations of animals.

The pneumococci which are found in healthy mouths are always of Type 4, except in persons who have been in contact with acute cases of pneumonia, when the type of organism with which that case is

27. Cole, R., and Dochez, A. R.: Trans. Am. Assn. Phys., 1913, xxviii, 606.

28. Dochez, A. R., and Gillespie, L. J.: Jour. Am. Med. Assn., 1913, lxi, 727.

29. Cole, R. I.: New York Med. Jour., 1915, ci, 1; Brit. Jour. Dis. Child., 1915, No. 135, p. 80.

30. Dochez, A. R., and Avery: Jour. Exper. Med., 1915, xxi, 114.

infected may be found. After recovery from an infection with one of the first three types, the organism disappears, and Type 4 reappears as a rule. In exceptional cases the original infecting organism may be found after recovery, but the longest time for which this has been observed was ninety days. Such persons are true carriers. Local changes in the lung are not necessary to make an individual susceptible to infection with the first three types, but are apparently necessary to start an infection with Type 4.

These facts have the greatest importance in the prognosis and treatment of pneumonia. By injecting a solution of sputum in salt solution into the peritoneal cavity of a mouse, and after four or five hours washing out the peritoneum with salt solution, and centrifuging, it is possible to get an abundant growth of pneumococci. The type of the organism can be determined by agglutination tests with the immune serum of Type 1 or 2, or by its morphology if it is of Type 3. If it gives no agglutination with the serums, and does not resemble the mucosus type, it belongs to Type 4.

When the type has been determined, much can be said as to the prognosis. As may be seen from the above figures, it is very good in Type 4, less good in Types 1 and 2, and very bad in Type 3.

[It has been a wonderful experience to be able to give a prognosis in several cases of acute pneumonia with the certainty which this work has made possible. In one case in a child, which lasted seventeen days, the organism was determined to belong to Type 4 and a good prognosis given throughout in spite of a severe infection. The prognosis proved to be correct. If it is true that most cases in children belong to Type 4, as seems likely from the findings in scattered cases in the various New York hospitals, it may be one of the factors which has made the prognosis so good in children.]

The treatment with serums is confined entirely to Types 1 and 2, which produce very active serums. Type 4 produces an active serum, but each one protects against the organism from which it was produced and that alone. The reasons for the failure to obtain any results of consequence in the past is very readily seen. If the disease is caused by Type 1 or 2, serum should be administered in large doses—80 c.c. every twelve hours. The effects of the serum may be judged by the effect on the blood cultures. When they are positive before injection, they become negative after it. The most satisfactory results are obtained with Type 1. In this group the mortality of patients treated with serum shows a marked reduction over nonserum cases. The results in Type 2 cases are not so encouraging, but pneumonia is a disease which varies greatly from season to season and it is impossible to draw any final conclusions until many more patients have been treated.

Peabody<sup>31</sup> found that in rabbits with a severe pneumococcus bacteremia the oxygen combining power of the blood falls progressively up to death. Coincidentally there is even a more marked fall of the oxygen content of the blood. This is due to the conversion of hemoglobin into methemoglobin.

Peabody<sup>32</sup> found that in most cases of lobar pneumonia the decrease in the respiratory surfaces is compensated for by the more rapid respiration, and the oxygen content of the blood is within normal limits. In occasional cases the oxygen content of the venous blood is low and the carbon dioxide content is high, due to interference with the respiratory exchange. In fatal cases there is a progressive diminution in the oxygen content and oxygen combining capacity. These cases usually have an intense bacteremia. There is a formation of methemoglobin, so that hemoglobin can no longer take up and give off oxygen easily. This is probably a factor in the immediate cause of death in many cases.

Wollstein and Meltzer<sup>33</sup> have produced an experimental pneumonia by the insufflation of various organisms into the trachea. Virulent streptococci always produced lobular pneumonia. The walls of the bronchi and the connective tissue framework of the lung were markedly infiltrated with leukocytes. This lobular bronchopneumonia occasionally fused to resemble lobar pneumonia, but there was very little fibrin in the exudate and no pleurisy. Pneumococci insufflated into the trachea in the same manner always gave a lobar pneumonia with a large amount of fibrin, no infiltration of the connective tissue framework, and was usually accompanied by a pleurisy.

Kline and Winternitz<sup>34</sup> found that in order to produce pneumonia in rabbits by insufflation it must be forcibly done, and the catheter must be inserted deeply into a bronchus, as insufflation into the trachea alone does not suffice. After administration of alcohol and exposure to cold, or inhalation of irritating gases, pneumonia was easily produced by insufflation of micro-organisms into the trachea alone. After section of both vagi, pneumonia results even without the insufflation of organisms. They think that possibly the predisposing factors act by their influence on the vagus control of the upper air passages.

Weill and Mouriquand<sup>35</sup> have made important studies of pneumonia by means of the Roentgen ray, and have done much to settle the long disputed questions concerning the diagnosis of lobar pneu-

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31. Peabody, F.: *Jour. Exper. Med.*, 1913, xviii, 1.

32. Peabody, F.: *Jour. Exper. Med.*, 1913, xviii, 40.

33. Wollstein and Meltzer: *Jour. Exper. Med.*, 1913, xviii, 548.

34. Kline and Winternitz: *Jour. Exper. Med.*, 1915, xxi, 304.

35. Weill and Mouriquand: *Lyon méd.*, 1912, cxix, 1018.



monia in infancy. The earlier writers affirmed the frequency of pneumonia but confused the different forms. A reaction followed and Parrot denied the existence of lobar pneumonia at early ages. This view prevailed throughout the profession with few exceptions until recently (Comby and D'Espine). The reason is that there has been no certain way to differentiate them until the perfection of Roentgenoscopy. Weill and Mouriquand's first report was of 52 cases of lobar pneumonia. Before the Roentgen ray, in twelve years they had records of only 19 cases, of which only 7 gave signs. Since the Roentgen ray they have had 33 cases, of which 31 gave positive shadows. Of these, 13 cases gave shadows before the appearance of physical signs, 18 cases had a shadow and signs at the same time, and two gave no physical signs at any time. The shadow in all the cases in the upper lobes was triangular, the base at the periphery, usually in the axilla, the apex at the root of the lung. In the lower lobes the heart and liver obscure the triangular form.

Weill and Mouriquand<sup>36</sup> believe that they can divide pneumococcus infection into three classes:

1. Pneumococcus infection without localization in the lung, which is the so-called "abortive pneumonia." This form gives all the general symptoms of pneumonia, the sudden onset, the typical temperature curve with a crisis, herpes of the hips (the vesicles containing pneumococci), and often a fibrinemia. There are no signs in the lungs except perhaps a few fugitive râles, and there is no shadow with the Roentgen ray. The duration is usually shorter than other cases but may be prolonged. These cases occur in the first and sometimes in the second year, and the prognosis is very good.

2. Pneumococcus infection with localization in the lung shown only by the Roentgen ray. This corresponds to the so-called "central pneumonia." With a typical shadow there may be no physical signs to the most careful and repeated examinations over the exact site of the shadow. Some of the cases may give signs late in the disease, but some have no signs at any time in its course.

3. Pneumococcus infections with shadow and signs at the same time.

The signs when present are often insignificant. A few fugitive râles and diminished vesicular breathing high in the axilla are often the only positive findings. The examination should be most careful where statistics have shown the localization to be most common, at the right apex, left base, right base, left apex. The physical signs are more frequent in the lower lobes; the cases without signs are

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36. Weill and Mouriquand: *Paris méd.*, Dec. 7, 1912, p. 17.

nearly always apical because the upper part of the thorax moves less with respiration and with partly occluded bronchi the signs are less apt to be transmitted. The general symptoms are usually present for three days before the shadow appears, and the appearance of the shadow is sudden and may be as late as the fifth or sixth day. Rarely there is a precocious localization in the lung, suddenly a part of one or more lobes becoming solid. Such a consolidation dominates the prognosis as in adults. The evolution of the shadow usually takes place in a characteristic manner. It begins at the periphery and extends inwards to the hilus of the lung, forming a triangle with its base in the axilla. At times the primary triangle spreads to involve the entire lobe, but in resolution the triangle reappears. The shadow persists two to three weeks after defervescence. Bronchopneumonia gives no shadow even when of the pseudolobar type.

Weill<sup>37</sup> has made further studies on the differentiation between lobar and bronchopneumonia of the pseudolobar type. He has found that there is practically no way of distinguishing these conditions clinically. Bronchopneumonia usually develops more slowly, there is often more general bronchitis, but atypical cases of lobar pneumonia may behave in the same way. He has noted that there is more commonly retraction of the suprasternal and substernal soft parts in bronchopneumonia, but this may occur in lobar pneumonia with a complicating bronchitis. An inverse type of respiration is frequently seen in bronchopneumonia—a type in which there is a pause between inspiration and expiration. There is seen a peculiar cough in about one-quarter of the cases, a short cough with each expiration for twenty to thirty minutes. All these symptoms may be seen in lobar pneumonia, especially when there is a severe bronchitis. Even the temperature curve may have an irregular form with wide excursions in lobar pneumonia.

The Roentgen-ray shadow differentiates the two forms absolutely. Further experience confirms the constant existence of the characteristic shadow in lobar pneumonia and the absence of shadow in bronchopneumonia, even when it involves a whole lobe and appears solid at necropsy. Occasionally a case occurs with all the clinical symptoms and with transient physical signs, but with no shadow. These are probably cases of congestion which do not go on to complete hepatization. Weill believes this, because he has found that the physical signs do not correspond exactly to the area of the shadow, but are more extensive, as if the congestion surrounding the hepatization were capable of giving changes in the percussion and breath sounds. [This

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37. Weill, E.: *Méd. mod.*, 1913, xxii, 1.

really makes a fourth type which should be added to those above, i. e., signs without shadow.]

At necropsy it is very difficult to distinguish the pseudolobar from the true lobar. Weill found that by injecting formaldehyd solution into the veins some hours before the necropsy, the lungs do not collapse, and the gross pathologic picture is much more true than when a collapsed lung is studied. In lungs studied in this way the triangular area of hepatization corresponds exactly to the Roentgen-ray shadow. The lobes affected by bronchopneumonia are never completely solid, but show lobular patches separated by more or less aerated lung tissue.

Mason<sup>38</sup> in a preliminary report demonstrated the character of the shadow in lobar pneumonia. He found that the shadow usually developed with the physical signs and cleared up at the same time with them. In all the early cases when the shadow occupied the periphery there was only dulness but when the shadow extended to the bronchi at the hilus, bronchial breathing appeared. Bronchopneumonia gave only a diffuse mottling; no sharp shadows.

Hartshorn<sup>39</sup> reports nine cases of pulmonary conditions, with illustrations showing how the Roentgen ray was useful in clearing up obscure diagnoses. These include pneumonia, tuberculosis, pleural effusions, lung abscesses, and pyopneumothorax. He calls special attention to the value of the Roentgen ray in early diagnosis of pneumonia, in which the shadows often show before the physical signs appear. The Roentgen ray shows the extent more accurately than does the physical examination.

Mouriquand<sup>40</sup> called attention to the diminution of expansion in the infraclavicular region on the affected side in pneumonia. This often lasts eight to fourteen days, and often helps in retrospective diagnosis. The prognosis of pneumonia is better in the cases in which the physical signs are not recognizable until late in the disease. This holds also for the advent of the triangular Roentgen-ray shadow. The frequency of complications he has found to be 7 per cent. of right upper lobe cases, 28 to 30 per cent. of lower lobe cases, while the left upper lobe cases, which are least common, have 60 per cent. complications.

Hutinel<sup>41</sup> holds that it is not enough to diagnose pulmonary inflammation, but that we should also differentiate between lobar and bronchopneumonia. In nurslings bronchopneumonia is the usual form,

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38. Mason: *Arch. Pediat.*, 1914, xxxi, 786.

39. Hartshorn, W. M.: *AM. JOUR. DIS. CHILD.*, 1915, ix, 405.

40. Mouriquand, G.: *Pathol. infant.*, 1912, ix, 71.

41. Hutinel, V.: *Rev. gén. de clin. et de therap.*, 1915, xxix, 49.

but it may be pseudolobar in type and resemble lobar in its symptoms, signs, evolution and sharp defervescence. After three years it is rare except as a result of the acute infectious diseases or with a tracheo-bronchial adenitis. It has a longer course, a more irregular temperature (which yields more easily to hydrotherapy, etc.), and greater dyspnea than lobar pneumonia. The Roentgen ray gives no shadow with bronchopneumonia, while lobar pneumonia casts a definite sharply outlined shadow.

The "abortive" cases which have all the initial symptoms but terminate in a few days with a sudden crisis, may possibly represent a pneumonia which goes only to the stage of congestion, with cure before hepatization. Hutinel has often observed tuberculosis following such an abortive attack. The prognosis of lobar pneumonia is nearly always excellent. It is rarely fatal except when complicated, and since the complication makes the prognosis so much worse, careful watch must be kept for otitis, meningitis, pericarditis, peritonitis, arthritis and nephritis.

Fleischner<sup>42</sup> thinks that the most common reasons for faulty diagnoses in lobar pneumonia are due to its frequent atypical nature, the absence of early signs, failure to make repeated examinations, and the difficulty of eliciting and interpreting signs in childhood. The most common signs are diminution of the breath sounds, increased crying voice, and slight dulness. He emphasizes the importance of light percussion, and the use of the Roentgen ray. He cites cases simulating meningitis, appendicitis, typhoid and empyema.

Pisek<sup>43</sup> in a preliminary report on 1,000 cases of pneumonia gives a mortality of 43.3 per cent. This is very high, but these were all hospital cases which are of the worst type. In the first two years of life bronchopneumonia predominated and was rare after the third year. Lobar pneumonia was much the more common after the third year, except in terminal or secondary infections, and is much more frequent than is usually supposed. Its cause was nearly always the pneumococcus. In the bronchopneumonias many different organisms were found.

Freeman<sup>44</sup> believes that pneumonia is rarely a lobar consolidation, and that bronchopneumonia is much the most common form in children, on account of the larger proportion of bronchi and the accompanying connective tissue. He describes the sequence as first a bronchitis, then peribronchial exudate, forming bronchopneumonic areas

42. Fleischner: *Arch. Pediat.*, 1915, xxxii, 165.

43. Pisek, G.: *Arch. Pediat.*, 1915, xxxii, 389.

44. Freeman, R. A.: *Am. Med.*, 1913, xix, 433.

which may fuse to form a lobar pneumonia. He thinks that in the bronchopneumonias of infancy there is often little bronchitis, and very frequently pleurisy. He does not believe in the usual classification for teaching purposes, but thinks that the distinction between lobar and bronchopneumonia need not be made. Pneumonia might better be presented to students as one disease with a sudden onset, with a persistent high or remittent temperature. The prognosis is good in primary cases in a healthy child. In secondary cases it should be guarded. With a persistent high temperature, pneumococcus infections are most common. With remittent temperature he suspects a mixed infection. With persistent high temperature a crisis may be expected; with remissions a longer course and lysis. The physical examination may or may not confirm diagnosis. Localized crepitant râles are the most common sign.

Thurlings<sup>45</sup> has summarized the whole matter of the existence of lobar pneumonia in infancy. Pathologists all consider that bronchopneumonia is much more frequent in infants and young children. Clinicians, however, agree that lobar pneumonia is not at all uncommon. This difference of opinion is explainable by the mortality statistics. In lobar pneumonia the death rate is from 1.5 to 5 per cent. and it is rarely fatal except in complicated cases. Bronchopneumonia is a very fatal disease and so comes to necropsy much more often in childhood than does lobar pneumonia; and it is on this occurrence on the necropsy table that pathologists base their statistics.

[This view certainly agrees with the usual experience in dispensary and private practice. It is very unusual to have a case come to a dispensary with bronchopneumonia, while lobar pneumonia is brought in every few days. The hospital figures do not represent the incidence of the two diseases because they deal with the worst feeding cases, marasmus, infectious diseases—all conditions which predispose to bronchpneumonia. That lobar pneumonia is not uncommon even in the hospitals, is shown by some recent figures from the Babies' Hospital:<sup>46</sup>

	Cured	Died	Mortality, Pct.
Lobar pneumonia on admission.....	52	1	1.9
Bronchopneumonia on admission.....	30	33	52.5
Bronchopneumonia acquired in hospital	3	13	81.0

In teaching students it is a regular experience, in showing a case of lobar pneumonia, to have it called bronchopneumonia, merely because it occurs in a child. It seems as if the recent evidence should do much to change the teaching of this subject.]

Dilatation of the nostrils in respiration in pneumonia is usually an active muscular phenomenon, according to Carducci.<sup>47</sup> This dilatation

45. Thurlings, M.: Dissertation, Freiburg, 1912.

46. Personal communication from resident physician.

47. Carducci, L.: Ref. in Arch. f. Kinderh., 1915, lxiv, 449.

occurs during inspiration. Passive motion of the nostrils, i. e., collapse during inspiration and dilatation during expiration, is a different matter and is seen only in fatal cases. It is not present in all fatal cases but when it is observed the prognosis is hopeless.

Hess<sup>48</sup> has studied the leukocyte counts in pneumonia. He believes that the primary pneumonias of infancy are lobar and that bronchopneumonia occurs only as a secondary infection or in infants of very low vitality. In spite of the low leukocyte counts in healthy infants, the reaction to pneumonia is very much the same as in adults. The leukocyte count depends on two factors—the reaction of the organism and the severity of the infection. Thus a high count indicates a severe infection and a strong resistance, a moderate count shows a slight infection with a good resistance or a severe infection with a poor resistance, and a low count shows a very slight infection or an overpowering one. A prognosis is impossible from the leukocyte count alone, but when taken in connection with the clinical symptoms it becomes of the greatest significance. The usual blood picture is a very high neutrophil count, and a moderate lymphocyte increase before the crisis. A deviation from this picture points to tuberculosis, typhoid, influenza or rickets. Very high counts should lead to a suspicion of empyema. The neutrophils rapidly disappear after the crisis, but the pseudocrises have no effect on the count. A slow fall with continued fever usually means delayed resolution or complications, but this is the regular behavior in secondary pneumonias. A sudden increase often points to the advent of a complication. The eosinophils disappear during the height of the disease and reappear just before or after the crisis. They have no value in prognosis, but their disappearance following a return makes a complication seem likely. In the secondary pneumonias the count varies and depends largely on the complications. Not infrequently the lymphocytes are high.

Baginsky<sup>49</sup> discusses the treatment of acute lobar pneumonia as a therapeutic paradigm. He cites the histories of several cases of typical pneumonia with crisis and recovery, in which the only treatment was rest, fluid diet and an ice bag to the region of the chest involved. He shows that interfering with the course of the disease is not necessary nor advisable, and greatly deplores the use of digitalis, aspirin, ipecac, apomorphin, camphor, etc., in such cases. Every unnecessary drug is harmful to a child, and also lacks the suggestive influence which comes into the question in adults. In childhood Nature battles more successfully alone. The doctor should watch and help, but only with

48. Hess: *AM. JOUR. DIS. CHILD.*, 1914, vii, 17.

49. Baginsky, A.: *Arch. f. Kinderh.*, 1915, lxiv, 190.

nursing, food, fresh air and cleanliness. The unweakened strength of the child's heart and his ability to manufacture the substances which produce immunity are ample to bring about recovery in the majority of cases. One case is cited which was treated by a younger associate, in which all sorts of needless remedies and therapeutic measures were used, and makes an excellent object lesson of what should not be done. The young physician should remember that the strength wasted in crying and struggling against therapeutic measures might better be saved to combat disease.

Freeman<sup>50</sup> injected six patients with antipneumococcus serum and nine patients with antipneumococcus and antistreptococcus serum. There were four deaths of the first six, and six deaths of the last nine. He concluded that the course of the disease was favorably affected in some cases but that the serum gave no result in most cases. In most of the cases there was a reaction and some improvement. The leukocytes were usually lowered and the polymorphonuclear cells were diminished in number. In the favorable cases there was little spreading of the disease and rapid resolution. The injected cases that recovered had a much shorter course than the controls, and the mortality was slightly less than the control cases. It seemed a safe method of treatment.

[In view of the recent advance of knowledge in regard to the different groups of pneumococci it is not strange that the serums have given such variable and unsatisfactory results. Freeman does not divide the cases into lobar and bronchopneumonias, and this may explain why the results were not better, for it is not to be expected that an antipneumococcus serum would influence a streptococcus bronchopneumonia.]

Delcourt<sup>51</sup> has treated twenty-four lobar pneumonias, and forty-two bronchopneumonias in private practice with continuous inhalations of oxygen. Only one patient with bronchopneumonia died, and the lobar cases all defervesced earlier than usual. It is necessary to be generous with its use, practically letting the child live in an atmosphere of oxygen. The expense is the greatest objection, since four to five thousand liters can be used per day.

#### SECONDARY AND BRONCHOPNEUMONIA

Hess-Thaysen<sup>52</sup> found that pneumonia of the first few days of life is much more common than formerly supposed. In thirty-two necropsies of children dying in the first three days, pneumonia was found in 14, or 42 per cent. He differentiates possible infections as,

50. Freeman: *AM. JOUR. DIS. CHILD.*, 1912, iv, 383.

51. Delcourt, A.: *Path. Infant.*, 1913, x, 64.

52. Hess-Thaysen: *Jahrb. f. Kinderh.*, 1915, cxxix, 140.

1. Placental infections—luteic infections, tuberculous or rarely pneumococcus, streptococcus or staphylococcus infections.

2. Aspiration pneumonias, either from aspiration of fetid uterine contents or the secretions of an infected birth canal. This corresponds to the old "septic pneumonia." But many cases also occur from aspiration of the secretions of a normal birth canal, or from aspiration of milk or even of mouth secretions.

3. Aerogenous pneumonias may occur, but must be very rare in the early days of life.

4. Metastatic pneumonia from a primary enteritis or navel infection.

The aspiration pneumonias are certainly the most common, especially the form which comes from the aspiration of bacteria containing secretion of the birth canal of a healthy woman. The bacteria found were streptococcus and colon bacillus as a rule. The fact that these pneumonias are found so early points to the fact that they must have begun during or shortly after birth. The clinical diagnosis is impossible, and even at autopsy the inflamed areas are often confused with atelectasis. Microscopic section shows pneumonia in many supposedly atelectatic areas.

Bonnaire and Durante<sup>53</sup> describe the inflammations of the lung due to infections of umbilical origin. They found miliary infarcts, zones of congestion, areas of hepatization, rarely abscesses, the bronchi usually normal. The symptoms are a few scattered râles, slight dulness, slight diminution in breath sounds; cough is rare, but there may be dyspnea or cyanosis. The diagnosis is difficult. An elevation of temperature or its recrudescence after a drop should lead one to investigate the lungs in a new-born, even when there is no manifest infection of the umbilicus. In 309 autopsies with umbilical infection sixty-two cases showed predominating pulmonary lesions. Only forty-one of these were recognized clinically. The umbilicus may appear normal or only very slightly infected.

Bassin<sup>54</sup> reports nineteen cases of pulmonary complications following operations on tonsils and adenoids, the infection taking place from inhalation of a fragment of tonsil or adenoid or blood clot. This may cause pneumonia, bronchopneumonia, abscess or gangrene of the lung. Great care should be taken to prevent inhalation accidents.

Riesman<sup>55</sup> describes seven cases of bronchopneumonia of a lobar form. The signs were all unilateral—dulness, bronchovesicular breath

53. Bonnaire and Durante: *Presse méd.*, 1913, xxi, 553.

54. Bassin, A.: *Thèse de Paris*, 1913, No. 181.

55. Riesman, D.: *Am. Jour. Med. Sc.*, 1913, cxlvi, 313.



sounds, and crackling râles. Temperature ran to 101 F. There was slight cough. The duration was several weeks up to four months. The prognosis was good, all recovering completely. These cases were thought to be confluent lobular pneumonia and are perhaps one cause of obscure fevers which is overlooked through careless examination. The protracted course and the fever lead to the suspicion of typhoid or tuberculosis. His treatment was counterirritation, the administration of creosote, a sedative cough mixture, careful feeding, rest and fresh air.

Suner<sup>56</sup> describes cases of bronchopneumonia with which are associated spasmodic symptoms which resemble laryngeal stenosis. The larynx is concerned in the symptoms even though there is no membrane, for the symptoms are relieved by intubation. In his cases streptococcus, pneumococcus and Friedlander's bacillus were the infecting organisms. In one case there was diphtheria of the bronchi but not of the larynx. They mostly occurred following measles or diphtheria. The symptoms were divided into three periods.

The first was a period of initial catarrh. There was a simple coryza, tracheitis, or bronchitis with fever of varying degree. This lasted usually two to nine days, but occasionally only a few hours. The second period was that of laryngeal stenosis. There was gradually increasing hoarseness, the voice became weaker and was gradually lost. Stridor supervenes with increasing dyspnea and cyanosis. The third period was that of asphyxiation. Death occurred if not relieved by intubation or tracheotomy.

This condition should always be considered in a bronchopneumonia, whenever there are symptoms of tracheitis, as it may rapidly go on to asphyxiation. The diagnosis is made by the initial catarrh in the presence of bronchopneumonia, the absence of membrane in the nose, throat or larynx, and the absence of Klebs-Loeffler bacilli from the culture. The prognosis is bad, especially in the rapid cases. Antitoxin should always be given as there is no time to wait for result of cultures. Intubation relieves the symptoms temporarily.

Comby<sup>57</sup> reviews the work of Suner and others and recommends the same treatment, but has found that the intubation allays symptoms only temporarily, because to the very serious inherent dangers of bronchopneumonia are added those of laryngeal stenosis.

Czerny<sup>58</sup> describes paravertebral pneumonias which occur in nutritional disturbances, in rickets and after measles. There are three theories as to the causes of this condition:

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56. Suner: *Jahrb. f. Kinderh.*, 1914, lxxx, 579.

57. Comby, J.: *Arch. de méd. des enf.*, 1914, xvii, 452.

58. Czerny, A.: *Jahrb. f. Kinderh.*, 1913, lxxix, 727.

1. Diminished immunity through nutritional disturbances;
2. Infection through a damaged intestinal wall;
3. Hypostatic congestion predisposing to pneumonia.

Disturbances of nutrition cause abdominal distention and pressure on the diaphragm. This gives lessened diaphragmatic breathing, which causes hypostatic congestion. In pathologic lessening of the intra-abdominal pressure the diaphragm becomes lowered, which also induces disturbed circulation in the lung. Through improved technic of feeding and prevention of inanition, the abnormal intra-abdominal pressure can be prevented and this is the best prophylaxis against paravertebral pneumonia.

Engel<sup>59</sup> found that paravertebral pneumonia occurs most commonly at the back part of the right upper lobe, and at the apex of the right lower lobe. In the left lung it is localized in the middle of the lower lobe, the upper lobe being usually free.

Arneth<sup>60</sup> reports excellent results from the use of hydrotherapy in the treatment of bronchitis and bronchopneumonia. His earlier practice was to use cool packs, with water at room temperature. These were given for a temperature over 40 C. for one-half hour; temperature over 39 C. for one hour; over 38 C. up to one hour and a half; and 38 C. to normal, two to four hours, three times a day. In cases with fever, packs were applied every three hours. In addition to this he laid stress on the necessity for a systematic change of position. The child should be turned on his side and also into the prone position at regular intervals. The prone position is important since the posterior part of the lungs is most affected by bronchitis, especially in helpless infants. It no doubt aids in preventing or removing atelectasis and stasis of the secretions. Strong children who have good muscular power and who react well stand cool packs well. Weaker children cannot stand the load of heat and their power of reacting is lost. Weaker children respond much better to warm baths and by his success with these children Arneth was led to use the warm baths with robust children as well, with surprisingly good results.

Mustard baths are not used at all, as they require much care and are not well borne by the sensitive skin of the child for long. He has practically abandoned medication except turpentine or oxygen inhalations, which are sometimes useful, but should not be used to the exclusion of hydrotherapy.

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59. Engel: *Verhandl. der Gesellsch. d. deutsch. Naturforsch. u. Aertze*, 1913, p. 10.

60. Arneth: *Deutsch. med. Wchnschr.*, 1913, xxxix, 1868.

His technic for the use of hot baths is as follows:

Water is used at a temperature of 41 C. (106 F.) and the temperature is kept up by adding hot water from time to time. With a fever up to 39 C. the duration of the bath is ten minutes; over 39 C., the duration is fifteen minutes. The child's temperature is lowered as a rule, but occasionally it is slightly higher immediately after the bath and drops after half an hour to an hour. The skin becomes red in the bath, in some children more than in others. There is rarely sweating, but the relaxed peripheral vessels allow the skin to radiate heat better than when the surface is cold. There seems to be less tendency for the temperature to reach its former height after warm baths than after cold ones. A favorable influence on the lungs and general condition is noticeable. The children do not object to the warm baths as they do to cold. They become less restless or less apathetic, look fresher and go to sleep usually after the bath. There may be slight temporary dyspnea at first in the tub, and after the bath the respiration remains deeper and slightly accelerated. At the end of the bath in stronger children one or two quick splashes with cool water are given to the chest and neck. The child is then dried and put to bed in warm clothing. The weight curves show good effects, children losing little or nothing in these tedious illnesses, probably because they lose less calories in the hot water than when treated with cold. The baths are kept up in convalescence once or twice a day, as it has been found that they prevent relapses. In acute coryza the hot baths are given but without the cold splash and the child is put into a hot pack after leaving the bath, to induce sweating.

Arneth believes that hot baths are a specific therapy for bronchitis and bronchopneumonia through the diminution of fever, the stimulation of expectoration, the prevention of atelectasis, and the tonic effect on the general condition. Since the use of the hot bath he has seldom lost a case, which is significant in these severe illnesses.

Stepp<sup>61</sup> also advocates the use of hot baths in the case of bronchitis and pneumonia in children. He has observed collapse from cold compresses and thinks that a jacket is inappropriate, merely oppressing the child by its weight on the chest. He also uses cold water on the chest, back and arms every two to three hours, except in weak children. He advocates prophylactic washing of the chest and back in the morning with cold water to prevent taking cold.

#### FIBROSIS AND BRONCHIECTASIS

Fletcher<sup>52</sup> considers that there are three factors in the forming of bronchiectasis; increase in intrabronchial pressure as in pertussis, the softening of the walls of the bronchi, as in bronchopneumonia, and traction on the bronchi as in fibrosis. The child's bronchus is thinner and softer than in the adult and hence is more susceptible to the factors that cause dilatation. Bronchiectasis is an acute condition in bronchopneumonia. It may be recognized by the persistence of coarse râles at the bases after the acute disease has subsided. It is more chronic in

61. Stepp: *Ref. Ztschr. f. Kinderh.*, 1914, vii, 536.

62. Fletcher, H. M.: *Clin. Jour.*, 1913, xlii, 363.

pertussis, and is frequently found, giving coarse râles and changes in the breath sounds over a localized area after the pertussis has ceased. The chief symptom is expectoration, and bronchiectasis should always be suspected when a child coughs up sputum. The râles often disappear entirely after coughing.

Pulmonary fibrosis may be localized or diffuse; the latter is the more common form in children. It may be due to congenital atelectasis, collapse of the lung from pleural effusion, obstruction of the bronchus or severe general bronchitis in young infants. Bronchopneumonia is the main cause, the inflamed areas becoming fibrotic. The prognosis is better in simple fibrosis than in fibrosis with bronchiectasis. There is usually progressive anemia from chronic absorption, lardaceous disease, tuberculosis or occasionally a cerebral abscess. A certain number of patients with bronchiectasis get entirely well. The treatment is hygienic and climatic. Emptying of the bronchiectasis by holding the child in an inverted position and making him cough prevents the absorption of the retained pus and does much to promote a cure. This should be done several times a day. Creosote inhalation seemed to have some value. Surgical drainage of these cavities is rarely successful, since they are nearly always multiple. Resection of a rib to allow collapse of the lung offers a better chance of success.

Miller<sup>63</sup> believes that measles, whooping cough and rickets are the most important causes of pulmonary fibrosis in children. Measles causes a characteristic form of fibrosis, a diffuse peribronchitis with a general widening of the smaller bronchioles. This picture is so characteristic that a skilled pathologist can make a diagnosis of measles as the primary infection. Pertussis distends the alveoli and bronchi causing emphysema and later bronchopneumonia which may become a fibrosis. Rickets predisposes to bronchitis and the softened ribs and weak muscles aid in causing slow recovery and permanent fibrosis. Under treatment, he emphasizes the importance of exercises, especially of the arms, and of making the child cough in an inverted position to empty the cavities. An occasional emetic is also useful in children who are too young to cough. The prognosis is bad; the cases become chronic lung cases, acquire tuberculosis or die of acute respiratory disease. A few grow up and are fairly well.

Hutinel<sup>64</sup> believes that bronchiectasis is not very infrequent in children. Bronchopneumonia damages and infiltrates the mucosa of the bronchi and sclerosis and bronchiectasis follow. It is especially common after pertussis, measles, influenza, chronic bronchitis, adenoids

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63. Miller, C.: *Practitioner*, 1912, xlv, 619.

64. Hutinel, V.: *La clinique*, 1913, viii, 50.

which provoke chronic cough, foreign body in the bronchi, compression of the bronchi by lymph nodes or a rupture of the softened lymph node into a bronchus, pleural adhesion, pulmonary sclerosis, tuberculosis, or syphilis. Bronchiectasis occurs in three forms: 1. Large, irregular cavities (usually due to sclerosis or pleural adhesions); 2. Fusiform or elongated cavities (following bronchopneumonia); 3. Cylindrical cavities. Physical signs are dulness, and diminished breathing over a localized area. If the patient takes a slight cold, many râles appear. The Roentgen ray shows an area of increased density surrounding a cavity. Tuberculosis is rarely a cause of bronchiectasis in children, since in them it is more often a caseating process rather than a sclerosing one (except in the case of mediastinal adenopathy). Syphilis, however, with its sclerosing tendency favors the production of cavities, and is often associated with a secondary tuberculosis.

The prognosis is not always bad, as small dilatations in infancy become relatively smaller as the growth of the bronchi takes place and may eventually become insignificant. These patients should have fresh air and live in the country on account of the danger of tuberculosis, and great care should be taken to prevent colds and secondary infections. Respiratory gymnastics and baths are useful.

Milhit<sup>65</sup> calls attention to the fact that bronchiectasis is not rare in children and may give no signs or symptoms until the advent of some acute catarrhal condition. The cavities are cleaner and less suppurating than in adults and tend to disappear with the growth of the lung. Among the causes, but by no means the only one, is hereditary syphilis. He cites three cases, verified by Wassermann, rapidly relieved by anti-syphilitic treatment, all signs completely disappearing. The diagnosis is difficult; all were thought to be tuberculosis at first. Diagnosis was made by the absence of tubercle bacilli and the negative von Pirquet, positive Wassermann, and by the Roentgen ray.

Bataille<sup>66</sup> reports twenty-three cases of obliterating adhesions of the pleural cavity. They are most frequently found in the second year, and are the result of a preceding acute or chronic disease of the lung or pleura. The thick sclerotic tissue firmly unites the lung and chest wall. This results in two types of cases, those with deformity of the chest and vertebral column, and those with respiratory and circulatory disturbances due to the involvement of the lung and mediastinum. The diagnosis is difficult as the symptoms simulate all the chronic diseases of the lung and pleura, and can only be made by careful study of the history, signs, and by the Roentgen ray. The prognosis is doubtful and

65. Milhit: *Arch. de méd. des enf.*, 1914, xvii, 105.

66. Bataille: *Thèse de Paris*, 1913, No. 367.

depends on the amount of mediastinal and lung involvement. The treatment is general hygienic measures, respiratory gymnastics, rest, and heliotherapy.

Lederer<sup>67</sup> believes that the beginning of chronic inflammations of the lungs in later childhood often goes back to infancy, and that many of these are not tuberculous. Their origin is in bronchitis or bronchopneumonia and often follows infectious diseases. The chronic process may end in an acute pneumonia or gradually change into an insignificant condition lasting for weeks or years. There may be complete recovery even after a long time, leaving only a small amount of fibrosis or mediastinal adenopathy. The prognosis is bad when there is extensive induration. The differentiation from tuberculosis can only be made by the course and by the Roentgen ray.

Sutherland and Jubb<sup>68</sup> believe that phthisis is rarer in children than is commonly thought, and that many cases so diagnosed are really chronic pneumococcus infections following pneumonia or bronchopneumonia, which leave a chronic bronchitis, bronchiectasis or fibrosis. They base this view largely on the failure to find tubercle bacilli in the sputum in children (only 9 per cent. positive cases), and on the positive finding of pneumococci in the sputum of many of these patients. They believe that cough with sputum, emaciation, following measles or pertussis should not be enough to make a diagnosis of tuberculosis when the sputum is negative. Even if the skin reaction is positive, it may occur from some other cause.

[The conclusion of these writers is based entirely on theoretical grounds; they give no pathologic evidence; nothing is said of the importance of fever, the character of the physical signs or the use of the Roentgen ray. The finding of the tubercle bacilli in the sputum of children is perhaps the least frequent diagnostic aid in tuberculosis in children.]

Pielsticker and Vogt<sup>69</sup> report ten cases of *artificial pneumothorax* in children. There were six cases of tuberculosis and four of bronchitis. The injection of nitrogen was well borne by most children. Their results were excellent, except in cases in which there were dense pleural adhesions which prevented the collapse of the lung, and this was true especially in the bronchiectasis. The tuberculous cases all did well.

Huber and Berkowitz<sup>70</sup> report a case of primary *actinomycosis* of the lung in a boy of 10. There were signs of consolidation of the upper right lobe, fetid breath and sputum. A diagnosis of gangrene

67. Lederer, R.: Jahrb. f. Kinderh., 1913, lxxviii, 68.

68. Sutherland and Jubb: Brit. Med. Jour., May 31, 1913.

69. Pielsticker and Vogt: Monatschr. f. Kinderh., 1912, xi.

70. Huber and Berkowitz: AM. JOUR. DIS. CHILD., 1914, viii, 113.

was made. Pus was obtained on aspiration and the lung was drained. The child died. The diagnosis was made only at necropsy and the condition was found to be due to the ray fungus.

Mauthner<sup>71</sup> reports a case of chronic bronchitis in a girl of 5. The sputum was greenish and contained a peculiar fungus hitherto undescribed. It was thought that the infection might have come from a pet turtle dove with which the child had been playing.

#### PLEURAL EFFUSIONS

Delhayé and Lawaese-Delhayé<sup>72</sup> have studied the cell count in pleural effusions. They found that the count does not definitely show the bacterial origin, but depends also on the intensity of the onset, the severity of the infection, and the time of puncture. Pyogenic organisms usually give a neutrophil increase, occasionally a lymphocytosis, and sometimes an eosinophilia. Tuberculosis tends toward a lymphocytosis, but occasionally the polymorphonuclears predominate. The nuclear formula of Arneth has not been higher in coccus infections than in tuberculosis, in their experience.

Weihe<sup>73</sup> has found that *interlobular pleural effusion* is not rare, having observed eight cases in two years. Only one of these was tuberculous, the rest metapneumonic. They occurred between the ages of 5 months and 3½ years. The effusion was small in amount in all cases; 3 c.c. was the largest amount obtained by puncture. The fluid was slightly turbid, due to the presence of leukocytes, but was sterile on culture mediums and animal injection. The diagnosis was made by the Roentgen ray which showed a narrow shadow, usually between the right upper and middle lobes. There was fever which suggested an empyema, but in no case was pus found. All of the patients recovered.

Mouriquand<sup>74</sup> calls attention to the importance of dullness at the base of the axilla in pneumonia. The percussion of pneumonia at the base, no matter how extensive, rarely gives dullness in the axilla or anterior part of the chest. Only the massive pneumonias give this dullness, and these are rare in infancy. A very small amount of fluid, however, gives axillary dullness. In all of thirty cases with this dullness, fluid was found on exploration. In cases in which resonance persisted at the base of the axilla, even when the auscultatory signs pointed to fluid, none was found on puncture.

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71. Mauthner, V.: Arch. f. Kinderh., 1914, lxxx, 341.

72. Delhayé and Lawaese-Delhayé: Bull. Soc. méd. d'Anvers., 1913, lxxiv, 185.

73. Weihe, F.: Ztschr. f. Kinderh., 1915, xiii, 119.

74. Mouriquand, G.: Pathol. inf., 1913, iv, 68.

## EMPHYEMA

Holt<sup>75</sup> reported 154 cases of empyema in children under 3 years of age. The mortality was 56 per cent., which seems high, but it must be remembered that these were all very young patients. The importance of age as a factor is shown by the mortality for each year.

First year, mortality.....	73 per cent.
Second year, mortality.....	58 per cent.
Third year, mortality.....	16 per cent.

The infecting organism influences the mortality greatly.

Streptococcus infections, mortality.....	79 per cent.
Mixed infections, mortality.....	62 per cent.
Pneumococcus infections, mortality.....	56 per cent.
Staphylococcus infections, mortality.....	50 per cent.

The leukocyte count was found to be high, as a rule, but varied from 6,000 to 81,000. There was no relation between the blood count and the type of infection, and it had no value in prognosis. The cause of death was usually sepsis and exhaustion, or some secondary infection, as pericarditis, meningitis, secondary pneumonia. Most of the cases were treated by simple incision, rib resection, or siphon drainage. Aspiration, and aspiration followed by the injection of various substances, were used in a smaller number, but the latter plan seemed to have no advantages.

Siphon drainage is the method of choice in the first year. The technic perfected by Kenyon was used. An exploratory aspiration is first performed. An incision is made with a small scalpel, large enough to permit the insertion of a rubber tube (size 27 French) around which is a collar to prevent slipping into the chest. The tube is strapped tightly to the chest wall with adhesive plaster, so as to make a tight joint, and is connected by means of a long rubber tube to a bottle under the bed. This bottle has a glass tube extending nearly to the bottom, and is kept half full of sterile salt solution, so that air can not enter the chest. The discharge is easily measured in this way, and varies from one to eight ounces a day. If the tube blocks, it may be cleared by "milking," or by raising the bottle and allowing the previously warmed salt solution to flow into the chest. This method has the advantage of avoiding the daily dressing with the struggling and fear of pain which it causes. It is a small operation and can be done under ethyl chlorid, local anesthesia, or even with no anesthetic. It favors expansion of the lung by preventing the entrance of air into the pleural cavity. Atmospheric pressure seems to prevent lung expansion in young infants. There is also less danger of secondary infection

75. Holt, L. Emmett: *Am. Med.*, 1913, viii, 381.



of the pleura with a sealed opening. If leakage of air takes place around the tube from ulceration, this plan may have to be abandoned and simple drainage used.

Next to siphon drainage, simple incision is best in infants. Rib resection is not necessary except in chronic cases or as a secondary operation where simple incision does not give good drainage. Aspiration occasionally cures a small empyema but is not to be relied on, and there is no advantage in injecting bactericidal substances into the pleural cavity.

Of the cases under 1 year there were:

Simple incision .....	16 cases, 3 recoveries
Rib resection .....	9 cases, 2 recoveries
Siphon drainage .....	20 cases, 8 recoveries

Savoriaud<sup>76</sup> gives a general summary of the symptoms and course of empyema and lays stress on the fact that the pneumonic are relatively more benign than the streptococcic infections. He gives the following indications for treatment: In tuberculous cases, aspiration only, as in a cold abscess, for incision means mixed infection and a persistent fistula. In mixed infections he recommends incision. In pneumonic effusions which have opened spontaneously into a bronchus, the treatment should be expectant. In pneumococcic empyema he recommends puncture if the case is mild, which may be repeated once, but if a third puncture is necessary, or if the patient does badly after the first puncture, it is better to incise. Staphylococcus or streptococcus infections or any fetid or gangrenous effusions must be incised at once. Incision is indicated whenever there are signs of septicemia. He describes only the technic of rib resection and evidently considers it the only form of operation. He does not give any figures to show his results.

In Dunlop's<sup>77</sup> experience empyema occurred in about 10 per cent. of the cases of pneumonia. He had a mortality of 19 per cent.; under two, 36 per cent.; over two, 13 per cent. Pneumococcus infections over two all recovered. He found the following organisms: pneumococcus, 53 per cent.; streptococcus, 16 per cent.; mixed infection, 14 per cent.; staphylococcus, 3 per cent.; tubercle bacillus, 3 per cent.

He lays stress on the point that latency of empyema usually means carelessness of the physician, and insists on the necessity for careful examination after pneumonia. The diagnosis must be made mainly by the percussion notes. The breath sounds are less reliable and the vocal fremitus is worthless in children as a diagnostic sign. He recommends aspiration in the very young, and also in very large effusions

76. Savoriaud: Jour. de méd. de Paris, 1913, xxxiii, 498.

77. Dunlop, H. G. M.: Edinburgh Med. Jour., 1914, xiii, 4.

the day before the operation so that a large amount of fluid need not be evacuated at the operation. Simple incision is good in very young children, as there is little shock and usually good drainage. His results:

Aspiration .....	8 cases, 1 death
Resection .....	61 cases, 14 deaths
Incision .....	29 cases, 5 deaths

Dowd<sup>78</sup> collected 285 cases of empyema with a mortality of 25 per cent. He divides the surgical treatment into diagnostic aspiration, methods of pus removal, treatment of chest after thoracotomy, treatment of complications. Aspiration for diagnosis requires a large needle and a good syringe. This seems simple, but good syringes are not by any means easily obtainable. Aspiration is not free from danger, as 25 deaths have been reported from this account alone. If one lung is incapacitated, aspiration of the opposite side may cause a pneumothorax and death. The pus removal is not a difficult operation. Ether should not be used as it is not well borne in pneumonia. Under a local anesthetic (novocain 1 per cent.) simple incision or rib resection may be easily done. Dowd prefers resection except in very young children. As soon as the pus is evacuated a coughing attack should be provoked if possible by irritating the pleura. The drainage of the chest is best promoted by a flanged spool, long tubes being inadvisable. A suction apparatus is not necessary. Blowing exercises during convalescence aid greatly in expanding the lung. Roentgenograms should be taken from time to time as there is frequently a secondary pneumonia or empyema of the other side. The danger of pocketing is much exaggerated as pockets very rarely occur. Northrup has never seen pus pocketed in a drained pleural cavity. A good deal of harm may be done in searching for pockets which do not exist, the complication really being pneumonia. A compressed lung which does not expand is the most serious complication next to pneumonia. If forced coughing and blowing exercises do not expand it, an enlarged thoracotomy and decortization of the lung may be done, and often effect a cure. Bronchial fistula may close spontaneously, or may require thoracoplasty and lung decortization.

Buttermilch<sup>79</sup> believes that puncture is better than rib resection in infants. The prognosis does not depend on the treatment entirely, but more on the course of the preceding or accompanying disease. The difference in malignancy depends on the virulence of the bacteria:

Simple puncture .....	3 cases, 2 deaths
Puncture and then resection.....	3 cases, 3 deaths
Resection .....	8 cases, 2 deaths

78. Dowd, C. G.: *New York State Jour. Med.*, 1914, xiv, 342.

79. Buttermilch, V.: *Ref. in Ztschr. f. Kinderh.*, 1913, vii, 102.

Stettin's<sup>80</sup> indications for operation depend on the virulence of the infection and on the strength of the patient. He advises rib resection in a strong child with a thick pus or when fluid reaccumulates after puncture. He uses puncture only in underweight or atrophic children, where there is very thin pus, in double empyema, or in polyserositis. Discussing Stettin's paper, Rietschl points out that so long as there is a pneumonia present, thoracotomy means death. Punctures should be used until the patient has recovered from the pneumonia, and then thoracotomy if necessary.

Hahn<sup>81</sup> recommends siphon drainage in children, especially in double empyema. He reports 80 per cent. cured with an average duration of twenty-five days. If the discharge persists after six weeks, rib resection should be done especially in sacculated empyema.

Werner<sup>82</sup> reports 178 cases of rib resection and drainage with 21 per cent. mortality, most all of which occurred in the first two years. He found that the pneumococcus infections had the best prognosis, mixed infections the worst. In a few cases he resected two ribs but the results were poorer and the healing slower.

Zingher<sup>83</sup> reports a case of bilateral empyema following acute bronchopneumonia in a child of 6½ years. The operation on the left side was done five weeks after the onset; on the right side eight weeks. The child recovered. He believes that the interval between opening both chests in empyema may be made shorter than is usually supposed. It has been done simultaneously with recovery. If only one side is done at a time, the left should be done first.

Nobécourt and Saint Girons<sup>84</sup> report an upper lobe empyema in a 14 month's child. It followed a mild pneumonia. There was fever, and dulness and signs of consolidation with Roentgen-ray shadow down to the nipple. On the fourth puncture pus was obtained which was dark colored, thick and showed pneumococci. Upper lobe empyema is rare in children. Only twenty-five cases in literature and only three in infants have been reported. The prognosis is good as all twenty-five recovered, with only one resection.

#### SUBCUTANEOUS EMPHYSEMA

Comby<sup>85</sup> gives the following causes of subcutaneous emphysema occurring in the course of acute respiratory disease: Lesions of the nasal fossae, the accessory sinuses, larynx, trachea (intubation or tracheotomy), foreign body or rupture of the bronchi, rupture of

80. Stettin, E. H.: Ref. in *Ztschr. f. Kinderh.*, 1913, vii, 101.

81. Hahn, B.: *Deutsch. med. Wchnschr.*, 1913, xxxix, 1830.

82. Werner: *Deutsch. Ztschr. f. Chirurg.*, 1913, cxxiv, 411.

83. Zingher, A.: *Arch. Pediat.*, 1913, xxx, 684.

84. Nobécourt and Saint Girons: Ref. *Ztschr. f. Kinderh.*, 1914, vii, 215.

85. Comby, J.: *Arch. de méd. d. enf.*, 1914, xvii, 81.

mediastinal lymph node, rupture of the lung tissue or of a subpleural tubercle. Rarely it may be caused by a lesion of the esophagus, stomach or intestine. The air penetrates the mediastinum, reaches the root of the neck and extends to the face and trunk. It is nearly always accompanied by dyspnea, cyanosis and coldness of the extremities, and often by fever. It may gradually disappear in from one to two weeks, or may cause death from asphyxia. The prognosis is bad in most cases, especially when there is tuberculosis or bronchopneumonia. The diagnosis of the emphysema is easy, no other condition giving the soft swelling with crepitation, but the diagnosis of the cause is more difficult and can only be made from the course and evolution of the primary disease. There is no treatment for the emphysema itself, but the dyspnea may need stimulation (digitalis or theobromin), oxygen, external heat to the extremities, antispasmodics, purgation, etc.

Delcourt<sup>86</sup> reports a case of bronchopneumonia of the pseudolobar type following measles, in which subcutaneous emphysema appeared on the neck and thorax. It gradually disappeared in about eight days and the child recovered. This is a rare outcome in emphysema with bronchopneumonia.

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86. Delcourt, A.: *Pathol. infant.*, 1913, x, 64.

## CURRENT PEDIATRIC LITERATURE

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### HYGIENE

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